"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

IDEALS

LOOKING through some early numbers of the *B.J.A.* we came across the following over the signature of the then editor, Dr. H. M. Cohen "The *B.J.A.* in passing into its third year is considering a move in the direction of advance. We believe that our matter should see the light of day as quickly as may be, and our aim is to make this possible by ultimately appearing every month. That is an ideal but, alas, it is not practicable at present. Nevertheless it is a star worth hitching our wagon to, and in the meantime it is desirable to attempt a compromise, that is to print an issue every other month. We believe that this will soon be feasible and ways and means to this end are being considered."

All of us when young have ideals. We feel that life would be perfect when we are top of the school, captain of the football team and the cricket XI. When in the course of time these ideals are reached! Well it's not quite what we expected; the flies in the ointment are different, but there are still flies. Tennyson puts it in more poetic form in answer to his own question: "And was the day of my delight as pure and perfect as I say? The very source and fount of day is dashed with wandering isles of night." So we learn at a very early age that an ideal, to be perfect, must be unattainable, for if and when we reach to what we supposed in imagination would be ideal, it isn't perfect. There are always flies or "isles of night". Dr. Cohen would no doubt be pleased that not only was the bi-monthly issue achieved in 1954 but his ideal, the monthly issue, followed in 1955. Were he to attend a meeting of our Board and listen to the criticisms and suggestions for improvement he would realize that he had set his ideal too low and that countless "isles of night" are still only too obvious.

Brit. J. Anaesth. (1956), **28**, 50

COMPARISON OF THE ELECTROENCEPHALOGRAPHIC PATTERNS DURING STEROID AND BARBITURATE NARCOSIS

BY

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A STEROID compound 21-hydroxy-pregnane-3, 20-dione sodium succinate (Viadril) has been used as an intravenous anaesthetic. The changes in the electroencephalogram produced by this agent have been observed by Boyan et al. (1955) to be similar to the changes reported by Kiersey et al. (1951) with thiopental sodium narcosis.

This study was undertaken to compare the electroencephalographic pattern of Viadril with that of short- and ultra-short-acting barbiturates and at the same time establish criteria for judging the depth of narcosis for these agents by employing the electroencephalograph. For comparison with Viadril ethyl-1, methyl butyl barbituric acid (pentobarbitone); isoamyl-ethyl-thio-barbituric acid (thiamylal); and an (N-) substituted barbiturate N-methyl - cyclohexanyl - methyl-barbituric acid (hexobarbitone) were selected.

METHOD

Thirty-six patients undergoing relatively minor surgical procedures were observed during this study. All patients were premedicated with atropine 0.4 mg and an appropriate dose of a narcotic one-half to one hour prior to anaesthesia. A 4-litre to 2-litre flow of nitrous-oxide oxygen was administered during the placement of frontocentral No. 25 needle electrodes. The patient was then allowed to breathe room air until no effect of nitrous oxide was apparent. Electroencephalographic tracings were recorded on a Grass III D electroencephalograph at a paper speed of 30 mm per second and calibrated for 50 microvolts at 7 mm deflection or 100 microvolts at 10 mm deflection. Oxygen was administered by mask and the intravenous agent in normal saline and water was injected intermittently until the desired level was observed on the electroencephalogram. A study of the patterns obtained in this series was then made by an examiner without knowledge of the agent used.

RESULTS

The changes in electroencephalographic pattern produced by the intravenous agents studied are similar. Therefore one description of the pattern of electroencephalographic changes will suffice for Viadril (fig. 1), pentobarbitone (fig. 2), thiamylal (fig. 3) and hexobarbitone (fig. 4).

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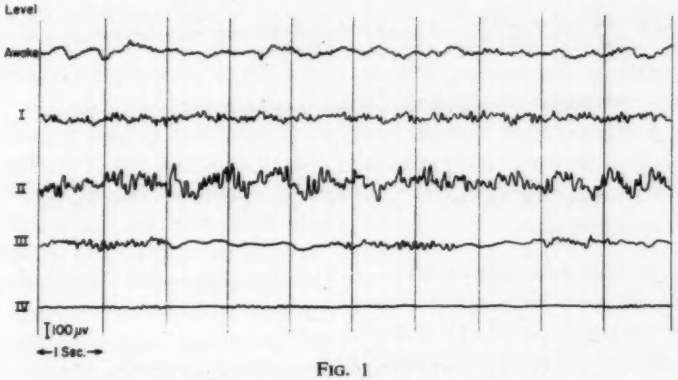

FIG. 1
Electroencephalographic pattern of hydroxydione (Viadril) anaesthesia

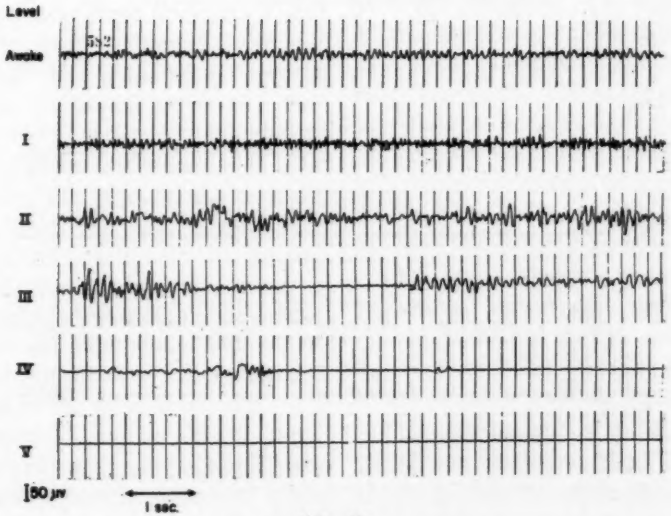

FIG. 2
Electroencephalographic pattern of pentobarbitone

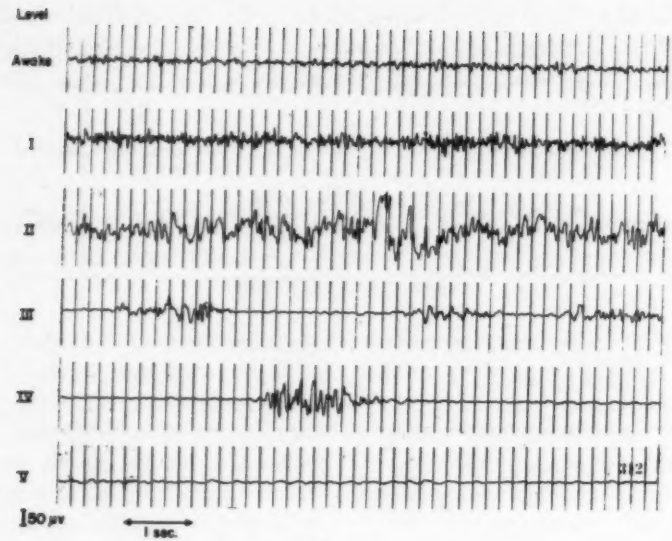

FIG. 3
Electroencephalographic pattern of thiamylal

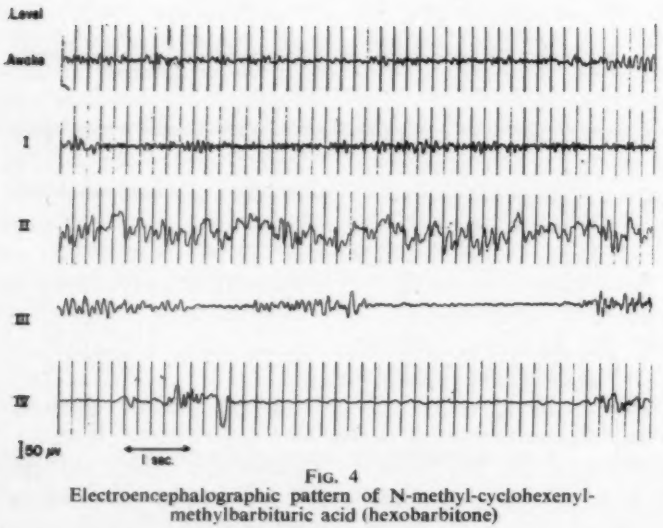

FIG. 4
Electroencephalographic pattern of N-methyl-cyclohexenyl-methylbarbituric acid (hexobarbitone)

The patterns have been arbitrarily arranged into four or five levels for ease in description and interpretation. Gradations appear between each pattern so that the change from one pattern to the next is gradual.

The first change that is observed from the awake pattern is an increase in frequency to 20 to 30 cycles per second. There may be a slight increase in amplitude. The patient at this time is drowsy.

As the amount of drug given is increased the pattern becomes of greater amplitude, spiky in nature and up to 200 microvolts in amplitude. The frequency is compound and consists of 20 cycle activity superimposed on slower 8 to 12 cycle activity.

The third level is characterized by silent areas or periods of " burst suppression " lasting one to three seconds. These silent periods were achieved with all agents studied. The areas of activity or " bursts " are composed of mixed frequencies, mainly 6 to 10 c/s with superimposed low voltage fast waves.

By increasing the amount of the agent administered level IV may be obtained. This level is arbitrarily set as having " burst suppression " of between 3 and 10 seconds duration. Patients with this degree of cortical depression will move upon surgical stimulation unless nitrous oxide is added to the inhaled oxygen.

Level V (level IV on the Viadril chart, fig. 1) is arbitrarily assigned to the electroencephalographic pattern observed when the duration of cortical suppression persists for 10 seconds or longer.

When the electroencephalographic patterns were compared it was not possible to detect characteristic changes that could be attributed to any one agent. All the intravenous agents studied produced the same change in the electroencephalographic pattern. However, at deeper levels it was possible to distinguish pentobarbitone records since the return from pattern four or five to pattern two was much slower than with other drugs studied.

DISCUSSION

The initial increase in frequency we have described with these intravenous agents has been observed by Brazier and Finesinger (1945), Derbyshire et al. (1936), Kiersey et al. (1951), Cohn and Katzenelbogen (1942), and Gibbs et al. (1937), as well as with diethyl ether anaesthesia by Bellville and Artusio (1955) and Gibbs et al. (1937). However, the fast activity produced by the intravenous agents appears to be less rhythmic and not as regular as the pattern observed during ether analgesia. The patients who exhibit this pattern (level I) with the intravenous agents may be conscious and react to pain in contrast to patients who are free of pain during ether analgesia. This lends support to the thesis of Derbyshire, Rempel, Forbes and Lambert (1936) that pentobarbitone suppresses cortical activity without blocking sensory paths leading to it, whereas ether blocks sensory paths before cortical activity is suppressed.

The mechanism of production of the initial increase in cortical frequency has not been entirely explained. Brazier and Finesinger discussed the possibility that it might be due to a change in membrane permeability or due to a depressant effect of the barbiturate on the dehydrogenase system. Torda (1953) attempted to relate

the increase in frequency and amplitude to acetylcholine content of the brain.

The slow waves that appear with surgical anaesthesia have been attributed to an alteration in function at the level of the reticular formation by French et al. (1953). It has been found that lesions in the reticular formation produce slowing of the cortical frequencies and a state of unconsciousness. Slowing is not necessary before unconsciousness is produced for it is possible with the intravenous agents as well as with ether to have unconsciousness without the presence of slow frequencies in the electroencephalogram.

The burst suppression or lack of cortical activity produced by the intravenous agents studied may be due to a direct effect of these agents on the cortex. Henry and Scotville (1952) have shown suppression burst activity similar to that obtained with thiopentone anaesthesia to arise from the isolated cortex. They postulate that suppression burst activity may be due to release of the cortex from the influence of the reticular activating system.

According to Gordan et al. (1951) the steroids act at a different site on the main line of biological oxidation than the other anaesthetic agents. However, except for its slow onset Viadril acts clinically, essentially like the intravenous barbiturates. Furthermore the electroencephalographic pattern changes appear to be similar.

Dawson and Walter (1944) have shown the limitations of visual analysis of the electroencephalogram. It appears from our studies that more detailed and precise studies of electroencephalographic changes during anaesthesia are necessary if the electroencephalogram is going to be of aid in understanding mechanisms involved in anaesthesia and narcosis. Important changes in electroencephalographic activity now occuring may escape interpretation that could be detected by electroencephalogram frequency spectrum analysis correlated with plasma oxygen, carbon dioxide and anaesthetic concentration.

SUMMARY

The changes in the electroencephalogram produced by 21-hydroxy-pregnane-3, 20-dione sodium succinate (Viadril); ethyl-1, methyl butyl barbituric acid (pentobarbitone); isoamyl-ethyl-thio-barbituric acid (thiamylal); and N-methyl cyclohexanyl - methyl - barbituric acid (hexobarbitone) are similar.

Viadril was kindly furnished through the courtesy of Chas. Pfizer and Company, Inc.

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Brit. J. Anaesth. (1956), **28**, 55

LOCAL ANAESTHETIC PROPERTIES AND TOXICITY OF HYDROXYPROCAINE AND HYDROXYAMETHOCAINE

BY

I. C. GEDDES*

ANAESTHETISTS and dental surgeons are constantly being urged to use a steady stream of new local anaesthetics for which superior properties are claimed. A recent review (Gray and Geddes, 1954) summarizes the information available on many of these.

In 1951 Grimme and Schmitz investigated a series of para-aminosalicylic acid derivatives in an attempt to find a tuberculostatic agent which would be more effective than para-aminosalicylic acid. Included in their series were hydroxyprocaine and hydroxyamethocaine (fig. 1) which were observed to possess local anaesthetic properties. Keil and Rademacher (1951a) reported hydroxyprocaine to be twice as effective as procaine with an increase of toxicity of one-fifth. In a further paper, Keil and Rademacher (1951b) found hydroxyamethocaine to be equal to amethocaine as regards anaesthetic potency, but only one-third as toxic.

Höller (1952), in a large series of uncontrolled dental cases, used a combination of 2 per cent hydroxyprocaine and 0.06 per cent hydroxyamethocaine, and claimed that this combination was more potent than hydroxyprocaine alone and superior to all known anaesthetics.

The methods used by the German investigators to substantiate these statements were such that it seemed desirable to reinvestigate the properties of these drugs prior to their release on the British market.

About this time a new local anaesthetic, lignocaine (fig. 1), was being widely used in Britain, and since preliminary reports were encouraging, it was included in the investigation for purposes of comparison.

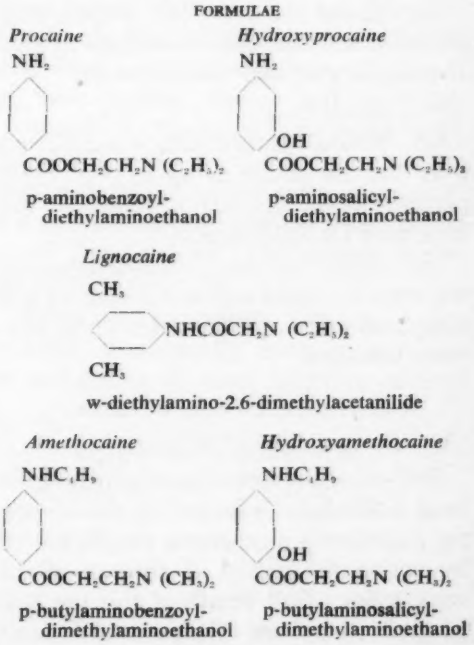

FIG. 1

* Written in the Department of Anaesthesia, Liverpool University, while working under a grant received from the Distillers Co. (Biochemicals), Ltd.

METHODS OF INVESTIGATION

(1) *Local anaesthetic potency.*

A preliminary survey of the literature on the methods available for testing local anaesthetics for duration of anaesthesia revealed that the majority of tests as such were far from satisfactory (Geddes, 1955). Two were, however, considered to be of value, namely, the corneal test in rabbits and the human intradermal weal test.

(2) *Toxicity tests.*

It is important to take into consideration both systemic and local toxicity.

(*a*) *Systemic toxicity.* Toxicity tests were performed in both mice and rats. Intravenous injection gave an index of the acute toxicity whilst intraperitoneal injection indicated the speed of absorption through the tissues.

(*b*) *Local toxicity.* The trypan blue irritation test was used in rabbits to give an index of the local tissue toxicity.

(3) *Clinical trials.*

(*a*) *Dental.* Information was collected from the use of the drugs in over 2,000 patients in the Extraction Clinic at the Liverpool Dental Hospital.

(*b*) *Major surgery.* Hydroxyprocaine was used for upper abdominal surgery and compared with a similar series where procaine was used.

(1) LOCAL ANAESTHETIC POTENCY

(A) *Corneal Test in Rabbits.*

Following the topical application of the local anaesthetic solutions to the cornea, the duration of anaesthesia was measured by noting the period of absence of the wink reflex. Full details of this test will be given elsewhere (Geddes and Evans). The experiments were designed to allow for sources of error attributed to variations between rabbits, between two eyes of the same rabbit and between day-to-day responses of the same eye. Four rabbits were used and the solutions were applied to the cornea for one minute. The order of instillation was tabulated in latin square designs and the test was repeated on each eye not more than once a day until each latin square was complete. The design chosen was a 2^3 factorial in two 4×4 latin squares. The anaesthetic, concentration, and pH being completely confounded between squares. Each complete latin square involved the application of solutions to 32 eyes. By using buffered solutions it has been possible to compare accurately the efficiency of the different anaesthetics at the two pH levels chosen.

Experiment 1. To compare 2 per cent and 4 per cent hydroxyprocaine hydrochloride with the same concentration of procaine hydrochloride at pH 5.5 and 7.4. Three latin square tests were performed and the results are given in table I, based on the application of solutions to 96 eyes.

Experiment 2. To compare 0.125 per cent and 0.25 per cent hydroxyamethocaine hydrochloride with the same concentrations of amethocaine hydrochloride at pH 5.5 and 7.0.

Hydroxyamethocaine, 4 per cent would not remain in solution at pH 7.4, but this difficulty was overcome by buffering to pH 7.0.

Five latin square tests were performed and the results given in table II are based on the application of solutions to 160 eyes.

The ratio of duration of anaesthesia with the fiducial limits are given in table III.

TABLE I
Comparison between procaine and hydroxyprocaine in corneal test. Rabbits

Anaesthetic (hydrochloride)	Concentration %	pH 5.5 Mean duration in minutes	pH 5.5 95% fiducial limits	pH 7.4 Mean duration in minutes	pH 7.4 95% fiducial limits
Procaine	2	0.42	0.00–1.84	14.20	6.60–29.50
Hydroxyprocaine	2	1.72	0.36–4.46	22.40	10.70–45.90
Procaine	4	2.51	0.75–6.03	35.70	17.30–72.50
Hydroxyprocaine	4	6.47	2.73–13.97	42.50	20.70–86.20

TABLE II
Comparison between amethocaine and hydroxyamethocaine in corneal test. Rabbits

Anaesthetic (hydrochloride)	Concentration %	pH 5.5 Mean duration in minutes	pH 5.5 95% fiducial limits	pH 7.0 Mean duration in minutes	pH 7.0 95% fiducial limits
Amethocaine	0.125	20.8	17.0–25.5	43.3	35.6–52.7
Hydroxyamethocaine	0.125	11.0	8.9–13.6	30.3	24.7–37.0
Amethocaine	0.25	30.9	25.3–37.7	51.5	42.3–62.6
Hydroxyamethocaine	0.25	23.3	19.0–28.4	37.8	31.0–46.0

TABLE III
Ratio of duration of anaesthesia with fiducial limits

Anaesthetics	Ratio	95% fiducial limits
Hydroxyprocaine/ Procaine	1.65	1.01–2.7
Hydroxyamethocaine/ Amethocaine	0.68	0.60–0.78

Thus, hydroxyprocaine gave a period of anaesthesia over one and a half times that of procaine, and hydroxyamethocaine seven-tenths of that given by amethocaine.

(B) *Intradermal Weal Test.*

The following points are considered of interest when using the intradermal weal test to compare duration of local anaesthetics.

(*a*) *Depth of nerve endings.* The sensory nerve endings of the skin have been separated into specific receptors for warmth, cold, touch and pain (Lewis, 1942). The spots identified as pain points may be segregated as closely as two hundred to the square centimetre in sensitive areas, but in others they are less frequent. Woollard, Weddell and Harpman (1939) described a method of locating the depth of these various sensory endings. This consisted of coating a fine needle with indian ink and inserting it into the skin until a particular sensation was aroused, and on withdrawal noting the length of the needle free from ink. The various depths are given in table IV.

When the anaesthetic solutions were injected intradermally, it was noted that on stimulating the weal, alteration of sen-

TABLE IV
Depth of various sensory endings.

Sensation aroused	Depth (mm)
Pressure	2.0–2.5
Touch	Surface contact 2.0
Cold	1.0–1.5
First or superficial pain	0.25–0.5
Second or deep pain	1.0 (average)

sation was present. A large, blunt aspirating needle was adopted as stimulator, for as each weal was stimulated six times at five-minute intervals, it was desirable not to cause damage. The use of a sharp needle left tender, bleeding areas due to penetration of the skin. No damage resulted from the use of the blunt needle which, however, was still capable of giving rise to a sharp sensation when applied to unanaesthetized skin. This sensation was termed "prick". When applied to anaesthetized skin, only a slight sensation of poorly localized pressure was felt. This sensation was termed "touch". The return of the "prick" sensation marked the end of anaesthesia. This end point was, however, somewhat subjective and not very precise.

Intradermal injection obtunded only the superficially located first pain endings and the deeper touch and pressure endings were unaffected.

(*b*) *Buffering of solutions.* Unlike the corneal test, alkalinization does not increase the potency of solutions when used for infiltration (Sollman, 1918). This was confirmed by Tainter (1941) who could find no evidence of difference between solutions of pH 5.4 and that buffered to pH 7.4.

(*c*) *Importance of isotonicity.* Braun (1924) observed that if solutions of sodium chloride were either hypotonic or hypertonic, irritation and pain resulted on intradermal injection. That this was due to altered tonicity was confirmed by injecting 0.9 per cent saline intradermally when neither pain nor irritation was noted. Sodium chloride was added to tonicity in all solutions used.

Procedure.

The solutions were made isotonic by the addition of sodium chloride, sterilized by heat and stored in alkali-free glass containers.

One-ml tuberculin syringes were tested for leaking by a modification of the method described by Guld and Rud (1953). The needles used were 26 gauge × ½″ with a short bevel. Both syringes and needles were dry-heat sterilized.

The flexor surface of the arm was shaved and swabbed with surgical spirit. The sites of injection were marked out in ink and 0.2 ml of each solution injected into the superficial layers of the skin. By careful positioning, it was found possible to make seven injections at approximately one-inch intervals along the forearm. Thus six local anaesthetics and isotonic saline for control were injected in the one volunteer, the blind test procedure being employed. Following injection, the weals were tested six times at five-minute intervals. The subject was warned that he would still be able to feel deep pressure and that a return of the sharp sensation or prick was sought. Onset of anaesthesia coincided with injection and this test is only of value for comparing duration of anaesthesia.

Intradermal weal tests were performed on 28 volunteers. The test was designed to compare:

(1) Procaine 2 per cent versus hydroxyprocaine 2 per cent.

(2) Amethocaine 0.06 per cent versus hydroxyamethocaine 0.06 per cent.

(3) Hydroxyprocaine 2 per cent versus hydroxyprocaine 2 per cent plus hydroxyamethocaine 0.06 per cent.

(4) Lignocaine 2 per cent was taken as the standard, for it gave the longest duration of anaesthesia in preliminary intradermal weal tests.

(5) By including normal saline, it allowed testing for the hydroxamethocaine and hydroxyprocaine interaction in a hydroxyamethocaine-hydroxyprocaine 2×2 table.

Statistical design of test.

The experimental design was in the form of a split plot arrangement with the sub-plots arranged in a latin square. In this type of design the number of replications must be equal to the number of sub-plot treatments. To enable this work to be carried out quickly on the one batch of solution, two operators each performed the test on half of the 28 volunteers.

The main plot treatments were the two experiments; the subplot treatments, the seven solutions; whilst the plots themselves were the individual "volunteers". Basically, the design consisted of seven replicates, each with two main plots, one for each experimenter (Cochran and Cox, 1950).

In the seven replicates, the subtreatments were the seven columns of a 7×7 latin square. In the complete experiment of seven replicates, two such latin squares were involved. Normally, in the analysis, the row sum of squares is merely eliminated, but in this case the rows have been made to correspond throughout with the seven sites of injection of the forearm taken in order, starting at the elbow and going down towards the wrist.

Since there were 28 volunteers, the whole experiment was duplicated.

Statistical analysis.

A previous intradermal weal test demonstrated that the method of measurement of duration of anaesthesia by noting the number of touches reported before the return of sharp sensation was the most accurate; it was adopted in this experiment. The results were assessed by the analyses of variance (Fisher, 1950).

Results.

The average number of touches for the six anaesthetics and normal saline, together with their fiducial limits, are given in table V.

TABLE V

Average number of touches for six anaesthetics and normal saline, together with their fiducial limits.

Anaesthetic	Concentration %	Average number of "touches"	95% fiducial limits
Procaine (hydrochloride)	2.0	26.7	23.7–29.2
Hydroxyprocaine	2.0	29.6	26.4–32.9
Amethocaine	0.06	14.1	12.0–16.4
Hydroxyamethocaine	0.06	10.9	9.0–12.9
Hydroxyprocaine + hydroxyamethocaine	2.0 + 0.06	28.6	25.5–31.8
Lignocaine	2.0	39.5	35.9–43.4
Saline	0.9	0.01	0– 0.16

Conclusions.

From this test it was concluded that a combination of 2 per cent hydroxyprocaine and 0.06 per cent hydroxyamethocaine could not be claimed to give a longer duration of anaesthesia than 2 per cent hydroxyprocaine. The average

for the mixture was actually less than for hydroxyprocaine, but the difference was not statistically significant ($p > 0.05$). There was a small difference between hydroxyprocaine and procaine (2.9 touches) but this did not reach statistical significance ($p > 0.05$).

Lignocaine was superior to hydroxyprocaine and procaine and the difference was highly significant ($p < 0.001$).

The difference between amethocaine and hydroxyamethocaine (3.2 touches) in favour of the former was also significant ($p < 0.05$).

These two latter comparisons can be expressed as ratios (table VI).

TABLE VI
Anaesthetic ratios

Anaesthetics	Ratio
Lignocaine/Hydroxyprocaine	1.3
Lignocaine/Procaine	1.4
Hydroxyamethocaine/Amethocaine	0.7

(2) TOXICITY TESTS

The five local anaesthetics were tested for systemic toxicity.

(*a*) *In Mice.*

Experiments were performed to determine the median lethal dose (LD_{50}). This has been defined by Gaddum (1933) as the mean of the smallest effective dose and the largest ineffective dose. Since the standard error of the deviation from the mean of any set of observations is inversely proportional to the number of animals used, the accuracy of determinations was dependent on the use of large numbers of animals. Albino mice were used for this test.

Procedure. Pilot tests were performed initially on groups of four mice, over a large range of doses, in order to establish the critical range over which some mice survived and others died. Having found the approximate level at which the LD_{50} might lie, four groups of ten mice, containing equal numbers of males and females and of as nearly as possible the same average weight, were carefully selected. Four dose levels graded on a logarithmic scale were injected in 0.5 ml of distilled water into the four groups of mice.

The percentage mortality was observed over a period of 48 hours after injection. In most cases, death occurred immediately, or within one hour of injection, depending upon the route of administration.

A repeat experiment was performed on the following day on another four groups of ten mice. If there was no close confermation in the results with those of the previous experiment, due to the error of sampling of animals, further experiments were repeated on the third and fourth days in order to reduce the standard error.

Tests have been performed with procaine, hydroxyprocaine, lignocaine, amethocaine and hydroxyamethocaine by intraperitoneal and intravenous injection.

Determination of median lethal dose. The given dose levels were calculated in mg of drug per kg of body weight and converted to logarithms. In order to avoid the sigmoid curve which results when these figures are plotted against the percentage mortality on simple graph paper, the mortality figures were first converted to "probits" by reference to standard tables (Bliss, 1938). The probit figures were then plotted as ordinates against the log dose in mg/kg as abscissae.

This procedure transforms the sigmoid dose response curve into a straight line which can be fitted more accurately and facilitates interpolation.

The LD_{50} was found by interpolation at the point where the regression line intersected the ordinate at probit 5. This log dose corresponds to a mortality of 50 per cent. The antilog of this gives the LD_{50} in mg/kg.

The calculated values have been obtained by weighing the observations statistically and calculating a more accurate regression line.

The LD_{50} values thus obtained are given in table VII.

(b) Intravenous Convulsive Toxicity Test in Rats

The minimum convulsive dose for procaine, hydroxyprocaine lignocaine, amethocaine and hydroxyamethocaine was determined.

The mean of the lowest dose which succeeded and the highest dose which failed to produce convulsions (in mg/kg) was taken as the minimum convulsive dose for each drug.

The results are summarized in table VIII.

The figures were found to be remarkably constant and the relative toxicities compared with procaine are of the same order as the intravenous LD_{50} values determined in mice.

Tissue Toxicity.

In determining local irritation, it is difficult to compare the results of different investigators since the degrees of irritation are arbitrarily assigned values depending upon the observer.

Coles and Rose (1929) made diagrammatic drawings of the rabbit's cornea and noted the following signs of irritation: inflammation of ocular and palpebral conjunctiva, pitting and mucus formation on the cornea and sclera. Pain need not

TABLE VII
Results of toxicity tests in mice.

Local anaesthetic	Intraperitoneal		Intravenous	
	LD_{50} mg/kg	95% fiducial limits	LD_{50} mg/kg	95% fiducial limits
Procaine	219.2	212.0–227.1	79.2	68.4 –85.6
Hydroxyprocaine	179.5	171.7–189.6	55.3	51.3 –62.0
Amethocaine	50.8	47.0– 56.8	10.0	8 83–10 27
Hydroxyamethocaine	99.7	93.1–103.9	33.4	31.6 –35.3
Lignocaine	122.4	101.9–131.3	34.6	32.7– 40.2

TABLE VIII
Results of intravenous convulsive toxicity tests in rats.

	Procaine	Hydroxy-procaine	Lignocaine	Amethocaine	Hydroxyamethocaine
Lowest dose which produced convulsions (mg/kg)	18.0	9.3	6.4	2.25	6.0
Highest dose which failed to produce convulsions (mg/kg)	21.4	10.0	7.6	2.0	8.0
Mean	19.7	9.7	7.0	2.1	7 0
Toxicity compared with procaine	1.0	2.0	2.8	9.4	2.8
Relative values obtained in mice	1.0	1.4	2.3	8.0	2.4

always accompany irritation. The different degrees of irritation, from engorgement of the capillaries of the conjunctiva to corrosive desquamation of the corneal epithelium, were noted on the diagrams.

Draize, Woodward and Calvery (1944) gave details of numerical scoring, enabling an evaluation of irritation to be made.

Meeker (1925) observed the tissue toxicity following intradermal injection in dogs' and rabbits' ears. He examined the weals in dogs microscopically after 24 hours and observed that procaine weals contained only a few lymphocytes and no coagulated exudates, as with more irritating compounds.

Hamilton, Westfall and Ferguson (1948) made intradermal injections in guineapigs of varying concentrations of local anaesthetics and noted the following reactions which were maximal after 24 hours: erythema, petechiae and ulceration with crusting.

Colloidal dyes such as Trypan blue and Congo red have been used for many years (Tainter and Hanzlik, 1924) to demonstrate increased permeability of capillaries. This test has been used by Hoppe, Alexander and Miller (1950) to assess irritation following intradermal injection of local anaesthetics.

Some authors claimed that the Trypan blue test could be used as provisional evidence for liberation of histamine by a given agent. Amethocaine in particular is capable of causing a flare in a large number of persons. Sonnenschein (1953) has shown that if the skin is previously infiltrated with procaine and then injected with histamine or amethocaine, no flare developed. He attributed this to blocking of the axon reflex by procaine.

The Trypan blue test was performed on rabbits following the procedure described by Hoppe, Alexander and Miller (1950). Three rabbits were shaved and injected with 0.2 ml of isotonic solutions of procaine, hydroxyprocaine, lignocaine, amethocaine and hydroxyamethocaine at the following concentrations: 4, 2, 1, 0.5, 0.25 per cent. Saline 0.9 per cent was used as a control. Fifteen minutes after intradermal injection, a 1 per cent solution of Trypan blue was injected intravenously by means of an ear vein. The dose was 1 ml/kg body weight. A blue colour appeared in some of the injected areas. Procaine and hydroxyprocaine gave a slight blue colour at 4 per cent level, but nothing at lower concentrations. Lignocaine resulted in a coloration at 2 per cent as well as at 4 per cent. Hydroxyamethocaine and amethocaine gave a blue coloration at all levels tested, but amethocaine produced a different picture in that a central pale area, surrounded by a definite blue halo, was observed. This central area ultimately ulcerated with scab formation during the following fortnight in the areas injected with 4, 2, and 1 per cent concentrations of amethocaine.

Of the five local anaesthetics, amethocaine is decidedly the most toxic locally. Hydroxyamethocaine did not produce necrosis and in comparison, lignocaine, procaine and hydroxyprocaine are considerably less toxic. These conclusions parallel the results found by the systemic toxicity tests.

(3) CLINICAL TRIALS

(*a*) *Dental.*

This trial was carried out in the Extraction Department of the Liverpool

Dental Hospital and has been the subject of a recent report (Mumford and Geddes, 1955). Sixteen different formulations were distributed and used on over 2,000 patients, the blind test procedure being employed throughout. The solutions were supplied in standard 2-ml dental cartridges and labelled with a batch number for identification. Each formulation was split into smaller batches which were issued at intervals to the Dental Hospital. If a batch was found to be of little value, it was relabelled and reissued. It was only withdrawn from the trial if rejected a second time. On many occasions, batches were used with no complaint after relabelling.

The values of the different formulae were assessed from the impressions recorded by the dentists and replies on prepaid postcards supplied to patients.

The general conclusions drawn from this dental trial are that no accurate reports are available to substantiate any claim of superiority between hydroxyprocaine and hydroxyamethocaine mixtures, and procaine. More importance would appear to be attached to the level of the vasoconstrictor in the solution. The longest duration of anaesthesia was observed when lignocaine was used.

(*b*) *Major Surgery.*

In a series of 71 gastrectomies performed under local anaesthesia, hydroxyprocaine 0.5 per cent was used on 43 patients and these were compared with a control series of 28 cases where procaine 0.5 per cent was used.

The solutions were dispensed in two bottles, one containing the local anaesthetic and adrenaline at an acid pH, while the second contained a phosphate buffer solution. When the two bottles were mixed in equal volumes, the resultant isotonic solution contained anaesthetic 0.5 per cent and adrenaline 1-200,000 at pH 7.4.

Anaesthetic technique. Premedication was with papaveretum $\frac{1}{3}$ grain (20 mg), scopolamine 1/150 grain (0.45 mg) one hour pre-operatively, followed by morphia $\frac{1}{4}$ grain (15 mg) prior to leaving the ward for the operating theatre. If the patient was aged 60 or over, the scopolamine was omitted and morphia $\frac{1}{6}$ grain (10 mg) was substituted for the morphia $\frac{1}{4}$ grain (15 mg). Following skin sterilization, 100 ml of local anaesthetic solution was injected in the skin and abdominal wall, including the recti muscles. This procedure took approximately five minutes, and following testing for anaesthesia the skin and linea alba were incised. No difference was noted in the speed of onset of anaesthesia with hydroxyprocaine when compared with procaine.

Once the peritoneal cavity was opened the abdominal wall was gently raised by hand and further solution, approximately 40 ml, was injected extraperitoneally to catch the intercostal nerves lateral the rectus muscle, thus anaesthetizing the parietal peritoneum. The coeliac plexus was next sought by gentle palpation, and by means of a long-guarded needle a further 40 ml of solution was injected close to the aorta which was retracted by means of the exploring fingers.

The vagus nerves at the cardiac end of the stomach were injected by direct vision, using approximately 10 ml of solution.

A total of 200 ml of 0.5 per cent solution was used and the resultant anaes-

thesia lasted for about 90 minutes. If the operation was not completed by this time, a further 40 ml was injected extraperitoneally on either side of the abdominal incision.

An attempt was made to estimate the duration of the anaesthesia by noting when further injections were required; these are more directly related to the operative procedure. On many occasions, further injections were not required until the intestines were being returned to the abdominal cavity, following the relatively painless completion of the anastomosis. No toxic symptoms were observed and many patients slept throughout the operation. In a few cases hiccough was noticed and this was treated by further injection of the vagi by para-oesophageal infiltration.

The general impression based on this series of gastrectomies was that hydroxyprocaine possessed equal anaesthetic properties to those of procaine.

CONCLUSIONS

(1) *Duration of Anaesthesia.*

(*a*) Hydroxyprocaine differs from procaine in giving slightly longer duration of anaesthesia on the rabbit cornea. This was not, however, confirmed by the intradermal weal test, where little difference existed between the two anaesthetics.

(*b*) The claim that the addition of 0.06 per cent hydroxyamethocaine to 2 per cent hydroxyprocaine resulted in increased duration of anaesthesia received no support from the intradermal weal test.

(*c*) Hydroxyamethocaine gave 0.7 times the duration of amethocaine anaesthesia for both the corneal and intradermal weal test.

(*d*) On the intradermal weal test, lignocaine gave a significantly greater duration of anaesthesia, namely, 1.4 times that of procaine.

(2) *Toxicity Test.*

When compared with procaine, the following approximate ratios for toxicities in both mice and rats were found.

TABLE IX
Results of toxicity tests in mice and rats.

	Mice		Rats
	Intra-peritoneal	Intra-venous	Intra-venous
Procaine	1.0	1.0	1.0
Hydroxy-procaine	1.2	1.4	2.0
Lignocaine	1.7	2.3	2.8
Hydroxya-methocaine	2.2	2.4	2.8
Amethocaine	4.3	7.9	9.4

(*a*) Hydroxyprocaine is 1.2 to 2 times as toxic as procaine, which conclusion must be compared with that of the German workers Keil and Höller (1952) who claimed that hydroxyprocaine was one-fifth to one-quarter as toxic as procaine, and Luduena and Hoppe (1952) who reported hydroxyprocaine to be 1.7 times as toxic as procaine following intravenous injection in mice.

(*b*) Amethocaine is between 4 to 9 times as toxic as procaine, and this is in agreement with the findings of Luduena and Hoppe (1952), who found it 8 times as toxic after intravenous injection in mice. Keil and Rademacher (1951b) gave the following toxicities for amethocaine and hydroxyamethocaine:

	Mice intravenous mg/kg	Rats intravenous mg/kg
Amethocaine	9.5	0.8
Hydroxyamethocaine	30.0	2.3

Thus the claim that hydroxyamethocaine is one-quarter as toxic as amethocaine has been substantiated.

Tissue Toxicity.

(*a*) Little difference exists between procaine and hydroxyprocaine, neither giving rise to any irritation, even at 4 per cent the highest concentration tested.

(*b*) Hydroxyamethocaine differs from amethocaine in not causing a halo effect or necrosis, as seen with amethocaine.

(*c*) Lignocaine at 4 per cent and 2 per cent concentrations gave rise to moderate irritation, as demonstrated by well-defined blue coloration in these areas. No irritation was observed at lower concentrations.

(3) *Clinical trials.*

Only negative conclusions can be reached from the clinical trials. No apparent advantages resulted from the substitution of hydroxyprocaine for procaine in either the dental trial or the series of gastrectomies reported.

In clinical work, so much depends upon the outlook of both surgeon and patient that it is debatable whether there is justification for more than generalizations when expressing opinions. If the surgeon has confidence in the drug under investigation, inefficient anaesthesia will be attributable to technical difficulties; otherwise the drug will be condemned as valueless. Bullock (1947), when investigating local anaesthetics, found that clinical trials were of little value as a basis for comparing local anaesthetics. Following extensive clinical trial of two local anaesthetic solutions by two experienced observers, both expressed diametrically opposite views. This is in accord with the inconclusive findings resulting from the present clinical trials.

SUMMARY

(1) Hydroxyprocaine has not been shown to possess any marked superiority over procaine and there would appear to be no justification for its introduction into clinical practice.

(2) The claims concerning the superiority of the combination of 2 per cent hydroxyprocaine and 0.6 per cent hydroxyamethocaine have not been substantiated.

(3) Hydroxyamethocaine, though not as active as amethocaine, is very much less toxic both systemically and locally, and it is recommended as a possible substitute for amethocaine for topical anaesthesia.

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UNIVERSITY OF CAMBRIDGE

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The Managers of the Frank Edward Elmore Fund will shortly award Studentships for medical research. The Studentships are open to male graduates of any University in any country, who were born at any place in the British Empire or Commonwealth other than in Scotland. Applications are invited from medically qualified graduates who are desirous of undertaking research, among other subjects, on problems of anaesthesia. The appointment will be for two years in the first instance at a salary of between £850 and £1,000 per year according to the candidate's experience, whether married or single, and other circumstances.

Applications accompanied by three testimonials, a statement of previous appointments and copies of published papers should be sent to the Regius Professor of Physics, Department of Medicine, Tennis Court Road, Cambridge, to reach him before April 25, 1956.

Brit. J. Anaesth. (1956), **28**, 67

THE ANAESTHETIC PROPERTIES OF 21-HYDROXYPREGNANEDIONE SODIUM HEMISUCCINATE (HYDROXYDIONE)

A Pharmacological and Clinical Study of 130 Cases

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THE anaesthetic potency of a series of steroid compounds was demonstrated in animals by Selye (1941 a, b; 1942 a, b). He stressed the correlation between anaesthetic action and hormone activity though admitting that exceptions existed to this general rule and one compound—Pregnanedione—had in fact no hormonal activity. Laubach, P'an, and Rudel (1955) studied the anaesthetic properties of certain steroids with a view to finding if any one was suitable for clinical application. From animal trials they suggested 21-hydroxypregnanedione sodium hemisuccinate (hydroxydione) as likely to be of value. It was water soluble, a potent intravenous anaesthetic, had a therapeutic index much in excess of thiopentone and no endocrine activity or other side effects to bar its clinical use. This compound was prepared by the Pfizer company under the name Viadril and administered intravenously by Gordan et al. (Murphy et al., 1955) to eight human subjects in doses up to 2 g. A clinical trial of the drug as an intravenous anaesthetic for surgery was then conducted by Murphy et al. (1955) who reported its use in 125 cases. They injected the drug slowly into the tubing of a freely running drip of dextrose solution. Concentrated solutions 2.5–5 per cent caused pain and were sometimes followed by phlebitis and thrombosis. In doses of 0.5–1.5 g they found it an effective basal anaesthetic. To produce full anaesthesia nitrous oxide and oxygen was usually required and frequently intravenous pethidine. For relaxation d-tubocurarine was used.

Through the courtesy of Organon Laboratories a supply of hydroxydione was made available for this study. The pharmacology of the compound was first examined in animals and isolated organs in the Department of Pharmacology and Therapeutics and it was then employed in a series of 130 patients as an intravenous anaesthetic. A full account of the pharmacology of hydroxydione will be published elsewhere but the following ex-

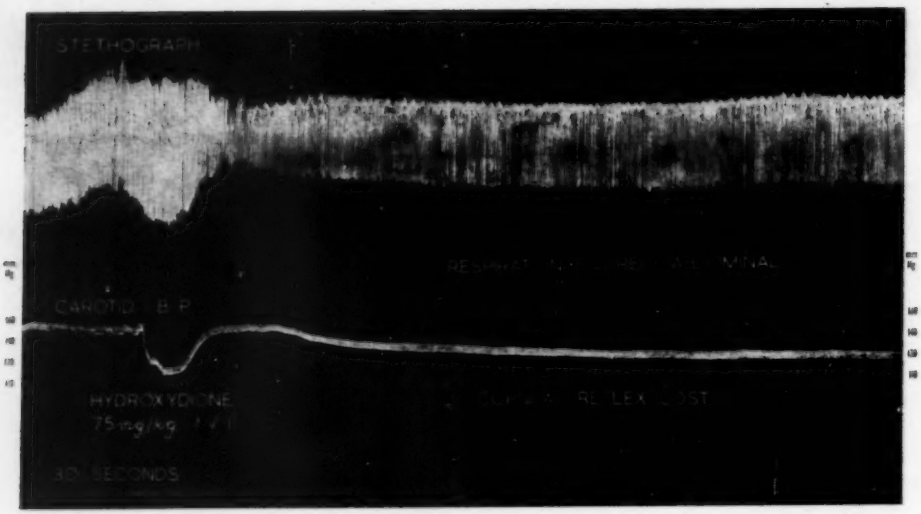

FIG. 1

Cat 2.5 kg. Right carotid artery and right femoral vein cannulated under light ether anaesthesia. Signal indicates injection of hydroxydione in normal saline by femoral vein.

periments are of particular interest to those in anaesthetic practice.

Animal Experiments.

It was at once evident that hydroxydione was irritant on intravenous administration. A rabbit would react vigorously to the injection of a 5 per cent solution into an ear vein. The following morning the surrounding tissue would be thickened and oedematous and the animal would resent handling of the ear.

In rabbits, not of a uniform strain, a dose of 40–100 mg/kg produced hypnosis and marked respiratory depression. Characteristically there was a delay of a few minutes before the effects of the drug became apparent. Hypnosis would last up to an hour and a half until the first spontaneous movement occurred. Doses above 100 mg/kg tended to produce respiratory paralysis. Following a dose of 100 mg/kg a rabbit would lie motionless and flaccid on the bench, sometimes with a respiratory rate below 40 per min (normal 150–200 per min). The corneal reflex, though sluggish, did not disappear and the animal would respond to squeezing the foot or pinching an ear. We concluded that in the rabbit the drug, in anaesthetic dosage, possessed hypnotic rather than analgesic properties.

An animal was then given a dose much above that causing respiratory paralysis and artificial respiration maintained for a prolonged period to determine whether survival was possible under these conditions.

Experiment. A rabbit weighing 2 kg was lightly anaesthetized with ether, an endotracheal tube passed with a Shadwell laryngoscope and the animal attached to a Waters' absorber outfit. 250 mg/kg of hydroxydione was given as a 2.5 per cent solution in 5 per cent dextrose intravenously over 3 minutes. Respiratory arrest was produced during the injection and

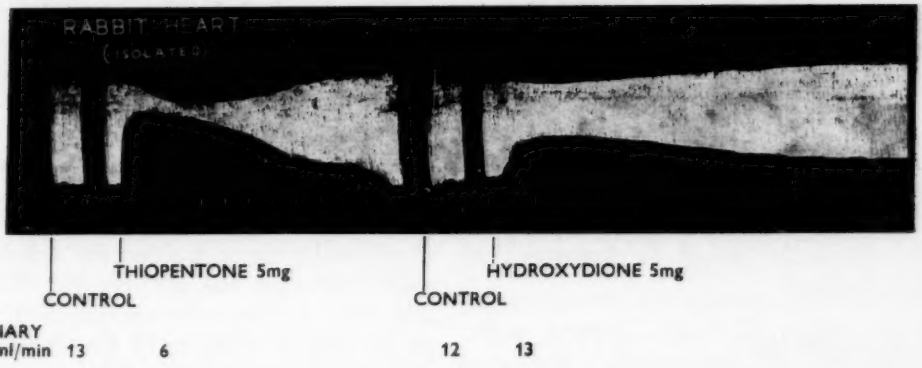

FIG. 2

Isolated rabbit heart perfused through the coronary circulation by Langendorff's method. The depressant action of equal doses of thiopentone and hydroxydione on injection into the perfusion fluid is shown. Time interval 30 seconds.

succeeded by a period of slow deep respirations lasting a few minutes. These increased in depth before subsiding to complete apnoea. Artificial respiration was begun before anoxia became severe, but in spite of this, the rabbit's circulation had collapsed and the cardiac impulse was almost imperceptible. Artificial respiration was continued; the circulation recovered and was apparently back to normal 45 minutes later. The earliest spontaneous respiratory movements did not occur until 80 minutes from the time of the injection. The animal was able to breathe without assistance 5 hours from the beginning of the experiment and had recovered completely by the following morning. It was alive and well 6 weeks later.

In experiments performed on cats, stethographic readings and carotid artery pressures were recorded simultaneously. A certain sequence of events followed the intravenous injection of 50–100 mg/kg hydroxydione, the drug being given in 5 per cent solution dissolved in normal saline. A dose injected over 15–30 seconds caused an immediate fall in blood pressure which returned quickly to its previous level (fig. 1). This was succeeded by a further fall in blood pressure which might take 15–30 minutes to reach its maximum and which usually returned to its control level as anaesthesia wore off. Respiratory depression, hypnosis and hypotension occurred pari passu with one another. Rapid intravenous injection of hydroxydione in cats was followed by immediate apnoea and convulsions.

While the concurrent onset of hypotension and central nervous system depression suggested that the main factor in the production of the hypotension was inhibition of the central vasoconstrictor centres, there appeared also to be a peripheral vasodilator action on the vessels themselves. Intravenous hydroxydione lowered the blood pressure of a pithed cat or one given a full dose of hexamethonium, but unlike hexamethonium appeared to have no significant action on autonomic ganglia.

Hydroxydione depressed the isolated rabbit heart but not to the same extent as thiopentone. Thiopentone caused an immediate depression of the amplitude of the contraction and reduction of the coronary flow. Both of these effects were soon over. The depression caused by hydroxydione was slower in onset, not so marked as that of thiopentone, and the duration of the effect was longer (fig. 2). The coronary

flow was usually increased. The depressant action of hydroxydione was entirely on the ventricular muscle. The drug had no significant effect on the isolated rabbit auricles, a property which it shared with thiopentone. Estimates of the depressant action of the two drugs on isolated rabbit hearts showed that thiopentone was approximately tenfold as depressant as hydroxydione.

Clinical Studies.

The drug was first used in a few cases for the induction of anaesthesia to get a general idea of its effect. It was then employed for a wide variety of operations (table I) in the general surgical, gynaecological, orthopaedic, thoracic and ear, nose and throat theatres. It was used over a wide age range, the youngest being 8 years and the oldest 75 years. Premedication in adults was morphine 1/6 grain (10 mg) and atropine 1/100 grain (0.6 mg) one hour before operation.

Dosage. Hydroxydione 0.5 g rendered the average adult very drowsy but rousable and not usually unconscious. One gramme made the average adult deeply unconscious. The dose was roughly judged to the physical state of the patient and the expected duration of the operation The maximum amount administered to any one patient was 2 g given in 9 cases to big well-built men. In other cases the dose was 0.75 to 1.5 g.

Supplemental anaesthesia. The only supplemental anaesthetic, where such was required, was nitrous oxide and oxygen. Occasionally the drug alone was sufficient when relaxation was not required. Usually, when the above dosage was used, the patient would appear to be deeply anaesthetized but would make some movement on stimulation. Nitrous oxide and oxygen then gave satisfactory operating conditions in all cases. This state of affairs, repeatedly observed, has led us to regard the drug much more as a hypnotic than an analgesic and can be correlated with the fact that in the series of cases by Murphy et al. pethidine was usually employed. If in an attempt to work under the drug alone with no supplemental anaesthetic the dose was increased, recovery was inconveniently long. When relaxation was required a muscle relaxant—d-tubocurarine or decamethonium iodide—was employed. The following are examples of typical dosage and procedures in average cases.

TABLE I
Dosage of hydroxydione

	Hydroxydione in grammes						Number of cases	Average dose
	0.75	1	1.25	1.5	1.75	2		
Upper abdomen	–	4	10	8	–	–	22	1.3
Lower abdomen	4	9	6	4	–	1	24	1.1
Kidney	–	–	1	2	–	1	4	1.5
Abdominal wall	–	3	6	6	–	2	17	1.4
Perineal	–	10	–	1	–	–	11	1.0
Chest wall	–	3	–	3	–	–	6	1.25
Intrathoracic	–	8	9	7	–	1	25	1.3
Extremities	–	–	2	7	2	3	14	1.6
E.N.T	–	4	–	1	–	2	7	1.4
	4	41	34	37	2	10	130	1.3

Dilation and curettage. Hydroxydione 1 g was usually sufficient without supplemental anaesthetic.

Mastectomy, ligation of varicose veins. Hydroxydione 1–2 g according to the vigour of the patient and the duration of the operation might be sufficient without supplemental anaesthetic. A smaller dose with nitrous oxide and oxygen gave as smooth an anaesthesia and a quicker recovery.

Appendicectomy. Hydroxydione 0.75 g. After the patient was asleep decamethonium iodide 5 mg was injected and anaesthesia maintained with nitrous oxide and oxygen 2 to 1 in a closed circuit without intubation, controlled respiration being continued as long as required.

Partial gastrectomy. Hydroxydione 1.5 g. After the patient was asleep d-tubocurarine 20 mg was injected followed by intubation with a cuffed tube. Anaesthesia was then maintained with nitrous oxide and oxygen 2 to 1 in a closed circuit, the patient being kept apnoeic with some hyperventilation and additional d-tubocurarine as required.

Intrathoracic operations such as lobectomy or segmental resection. Hydroxydione 1–1.25 g followed by d-tubocurarine 20 mg. Intubation with cuffed tube. Nitrous oxide and oxygen 2 to 1 in closed circuit, the patient being maintained apnoeic with additional d-tubocurarine as required.

Technique of administration. Venous thrombosis was the outstanding trouble and affected the method of administration. Hydroxydione can cause pain on injection followed by painful phlebitis and a thrombosed vein extending up the arm as far as the vein can be palpated. In the first twenty cases the drug was given in a 1.25 per cent solution in 5 per cent dextrose saline. This caused discomfort unless the rate of injection was very slow, and venous thrombosis was frequent. In all other cases the drug was given in 0.5 per cent solution in 5 per cent dextrose in distilled water. This necessitated 300 ml of fluid to give 1.5 g and a freely running drip through a fairly large-bore needle to give the solution in 2–5 minutes. Such a procedure tended to make the induction of anaesthesia cumbersome for less major cases. On the other hand for major cases where the patient arrived in the anaesthetic room with a running drip, it was no disadvantage. In some later cases a three-way tap assembly was used in a manner similar to that once recommended for the barbiturates. This enabled the hydroxydione to be given very smoothly.

Five per cent dextrose solution was used as the vehicle following the practice of Murphy, though it was appreciated that this in itself might increase the possibility of thrombosis. The solution being run in rapidly, it was warmed before dissolving up the hydroxydione. Complaint of discomfort on injection was very rare. It was assumed that Murphy used the dextrose solution because of its buffering action against the alkaline hydroxydione. The pH of 0.5 per cent hydroxydione in distilled water was found to be 8.0, and that of 0.5 per cent hydroxydione in 5 per cent dextrose in distilled water to be 6.98. Venous thrombosis was due to the irritant action of the hydroxydione and not to the pH of the injected solution.

Delay in action was quite definite but varied with the dose, rate of injection and vigour of the patient. When 1 g was given

over 2 minutes the patient might not admit any effect for 2 minutes after completion of the injection but was very drowsy within 3 minutes and unconscious within 4 minutes. Another might be asleep 1 minute after completion of the injection while a vigorous man would still be trying to respond to questions 5 minutes later. Eventually he would be unrousable. The onset of unconsciousness was as near to falling asleep as one could wish. The patient might volunteer that he was feeling drowsy but even this was rare. The full effect was not reached with unconsciousness. With increasing experience one tended to wait 5–10 minutes after the onset of unconsciousness before attempting intubation or taking the patient into the theatre. Delay in action makes a technique involving additional doses troublesome. With thiopentone one can inject an additional dose as required, but this is not so easy when one has to run in a large volume of fluid and wait for it to be effective.

Intubation. After 1–1.5 g hydroxydione the average adult was deeply unconscious, the lower jaw relaxed, and unattended the tongue might fall back and the patient be completely obstructed. A laryngoscope could be inserted and the larynx visualized with the same ease as in deep anaesthesia or after an adequate dose of relaxant. The cords were usually found widely abducted. There was no difficulty with intubation but the patient reacted vigorously. In the average case he soon settled down and tolerated the tube unless the head was disturbed. The reaction to the tube could of course be prevented by spraying the cords with local anaesthetic after visualizing the larynx.

Relaxation. In the dosage used the jaw muscles were relaxed but abdominal relaxation was not obtained, at least of a degree anything like sufficient for abdominal surgery. A surgeon attempting an appendicectomy under hydroxydione with nitrous oxide and oxygen would complain of complete rigidity. Compared with cases done under thiopentone–nitrous oxide and oxygen, any reduction in the dose of relaxant necessary was not found.

Respiratory depression was not marked. After hydroxydione 1–2 g the respiration was reduced in volume but even with 2 g apnoea was unusual. In operations carried out with no supplemental anaesthetic or with nitrous oxide and oxygen, the surgical stimulus increased the depth of respiration.

Effect on the circulation. In four cases electrocardiograph records were taken during the injection of hydroxydione 2 g and for 10 minutes after completion of the injection. In no case were there any arrhythmias. Pulse rate and blood pressure records showed great variability. The pulse rate usually rose as the injection was begun. This was due in part to the large volume of fluid injected rapidly but was greater than one would expect from this cause alone. When the injection was finished the pulse rate tended to drop towards normal but any stimulation such as intubation or operation might maintain it at a high level. During operations under hydroxydione a five-minute pulse record often ran at a higher level than one was accustomed to record, the pulse rate settling down when the operation was completed (fig. 3). It may be suggested that this is inadequate anaesthesia and

reinforces the view that hydroxydione is more a hypnotic than an analgesic. In a healthy young adult the effect of hydroxydione on the blood pressure was not marked but in a middle-aged or older subject the blood pressure was usually reduced. A moderate fall to the 80–90 mm Hg systolic level was not infrequent (fig. 4) and a drop to the 50–60 mm Hg systolic level could occur. The fall in blood pressure was not precipitous and might not be complete till 15 minutes after the injection of the hydroxydione. A large drop in blood pressure was recorded on five occasions and in each case the patient was aged 60 years or over. Figure 5 is an example in a patient aged 70 years undergoing operation for the radical cure of a large hydrocele. He had a pre-operative blood pressure of 200/110 mm Hg and hydroxydione 1 g was the sole anaesthetic, the patient only inhaling oxygen. When such a blood pressure drop occurred it was not raised to any extent by adopting the Trendelenburg position but was raised by the injection of Methylamphetamine. When the blood pressure dropped to a low level the pulse rate was usually slow. Because of this hypotensive effect hydroxydione was not used in patients undergoing operation after resuscitation from shock.

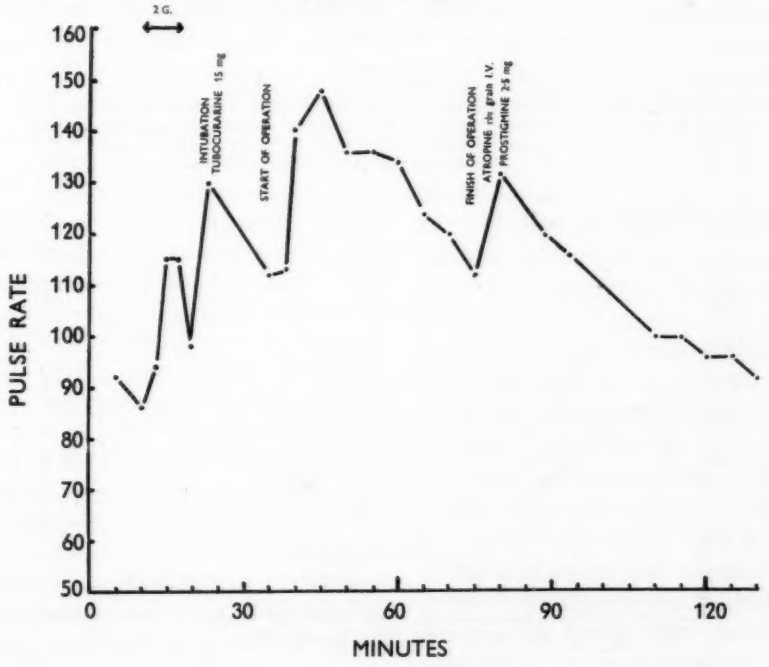

FIG. 3

Partial nephrectomy. Male aged 32 years under hydroxydione 2 g, tubocurarine 15 mg, with gas and oxygen 2/1 in closed circuit. Premedication: morphine 1/6 grain (10 mg) and atropine 1/100 grain (0.65 mg) one hour before start of record.

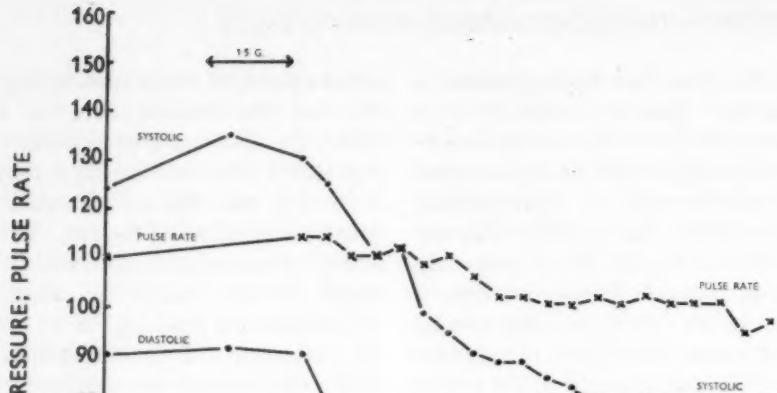

FIG. 4

Fall in blood pressure in a female patient aged 55 years given 1.5 g hydroxydione. The patient was not taken into theatre until completion of the above record. The effect is therefore seen uncomplicated by operative stimuli. Premedication: morphine 1/6 grain (10 mg) and atropine 1/100 grain (0.65 mg) given one hour before the commencement of the record.

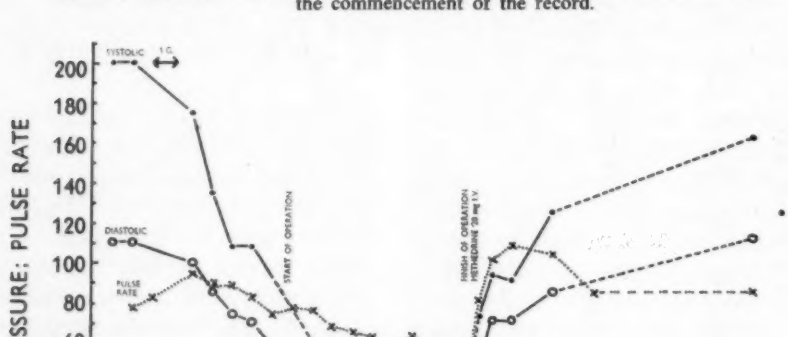

FIG. 5

Marked fall in blood pressure in a hypertensive male patient aged 70 years undergoing repair of a hydrocele. Hydroxydione 1 g was used without supplemental anaesthesia. The patient was given oxygen throughout the operation. At the end of the operation there was slight movement at each skin stitch. Premedication: morphine 1/6 grain (10 mg) and atropine 1/100 grain (0.65 mg) administered one hour before the start of the record.

Recovery time. This varied so much from one patient to another that one can only speak generally. After hydroxydione 1 g one would expect an average adult to be awake and rational but still drowsy at the end of one and a half hours.

Blood sugar. The effect on the blood sugar was observed in one case given 1.5 g and in two cases given 2 g hydroxydione. Estimations were done before and every 15 minutes for three-quarters of an hour after the injection, the patient being kept in the anaesthetic room until the tests were completed. In no case had the drug any effect on the blood sugar.

Excretion. In two cases (young males) a sample of urine was obtained immediately before going to the theatre, and the first urine passed following operation was also collected. A naphthoresorcinol reaction (Hawk et al., 1949) was performed on 5 ml of each specimen, both tubes being handled together. In both cases the violet red colour developing in the postoperative specimen was markedly deeper than that of the pre-operative specimen, and appeared to be more intense than could be accounted for by the increase in the concentration of the postoperative specimen. This was interpreted as an increase in urinary glucuronates possibly due to the excretion of hydroxydione conjugated as a glucuronate but no confirmatory tests were performed.

Complications. There were the usual respiratory ones which may accompany any anaesthetic. After an adequate dose the tongue might fall back and the patient completely obstruct unless the jaw was supported or an airway inserted. With the dosage so far used ventilation was usually sufficient but occasionally it was depressed and the patient required oxygen or inflation to maintain colour.

Twitching of one or more limbs, almost of a convulsive nature, occurred occasionally. In the present series this was noticed on six occasions and ceased when nitrous oxide and oxygen was begun. This twitching might appear spontaneously or result from stimulation. In one case who had hydroxydione 1.5 g the operation was not possible under the hydroxydione alone because of the convulsive twitching of the limbs which any stimulus elicited.

A moderate drop in blood pressure was not unusual and a large fall in blood pressure might occur. This large drop typically occurred in older subjects.

Venous thrombosis was the outstanding trouble, and even when the hydroxydione was given in 0.5 per cent solution it still occurred. Usually it was found only on examination but occasionally the vein might stand out on the arm as a thick knotted cord of which the patient complained. After the injection of hydroxydione great care must be taken to see that no venous obstruction occurs in positioning the patient. Such obstruction may cause the vein to be seen or felt during operation, already thrombosed, as a thick rubbery cord. Even the obstruction produced by a sphygmomanometer cuff has caused such thrombosis. Using 0.5 per cent hydroxydione in 5 per cent dextrose in distilled water, and not including cases in which the intravenous infusion was continued for some time postoperatively, there were 70 cases in which it was quite definite whether the vein was or was not thrombosed. Thrombosis had occurred in 15 cases.

COMMENT

One naturally compares hydroxydione with thiopentone. In minor surgery there is with hydroxydione delay in induction and recovery, making its use too time consuming. In abdominal and thoracic surgery hydroxydione–nitrous oxide–oxygen–relaxant gives as smooth an anaesthesia as thiopentone–nitrous oxide–oxygen–relaxant, with the advantage that hydroxydione gives a longer basal anaesthesia and a repeat injection is seldom required. On the other hand the patients will not usually be so ready to wake up in theatre if such is desired.

It may be suggested that the lack of any profound respiratory depression with hydroxydione is an advantage. In abdominal and thoracic surgery this is not of much moment, the patient in modern practice being maintained apnoeic in any case. In less major surgery, too, it is easy to cope with any temporary acute respiratory depression from thiopentone. Only in the Ear, Nose and Throat Department has the lack of respiratory depression been found an advantage. Here the jaw relaxation with adequate respiration may give hydroxydione a place. It gives a smooth anaesthesia for laryngoscopy, the larynx being easily visualized and the cords found wide apart. If a biopsy has to be taken the cords must be sprayed with local anaesthetic and this is conveniently done after the hydroxydione injection with no discomfort to the patient. Time must then be given for the local anaesthetic to be effective, but such time is available with hydroxydione. For bronchoscopy, too, it is effective, but the local preparation must be as thorough as when local anaesthesia is to be used alone or the patient will react vigorously during the examination. In both these procedures the delay in recovery is unfortunate.

With methods already available, which enable the patient to pass comfortably to sleep, which give the surgeon complete relaxation when necessary, and which allow the patient to regain consciousness in the theatre if such is desired, any new anaesthetic must have advantages to justify its introduction. Hydroxydione starts off with the disadvantage that induction is cumbersome, requiring a freely running drip or a three-way tap assembly. Postoperatively venous thrombosis may occur. Even with these disadvantages hydroxydione is of interest. If means were found of injecting it from a syringe in concentrated solution without fear of thrombosis it could rival thiopentone for a variety of procedures, and if not it may be the forerunner of a new class of anaesthesia.

ACKNOWLEDGMENTS

We are grateful to Professor Hunter for suggesting this study and for his helpful criticism in the preparation of this paper; to Dr. Hamish Watson for electrocardiograph records; to Dr. Gemill Morgan for blood sugar and pH estimations; and to the various surgeons who endured the earlier trials.

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Brit. J. Anaesth. (1956), **28**, 77

ANAESTHESIA FOR ADRENALECTOMY

BY

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CADE (1954) indicated that the adrenal gland is composed of an outer cortex, essential to life, which produces hormones controlling carbohydrate, protein and electrolyte metabolism, and the medulla, which secretes adrenaline and noradrenaline. Surgery of the adrenals consists of partial or total removal of one or both glands or tumour, performed at one operation, or in two stages with about three weeks between each adrenalectomy, and involves replacement of the hormones with desoxycorticosterone acetate, cortisone and short-term administration of noradrenaline. Successful bilateral adrenalectomy was first performed in 1945 (Huggins and Scott) following the discovery and synthesis of cortisone, who with Bergenstal (1951, 1952) reported further successes.

Total Adrenalectomy.

Bilateral adrenalectomy is performed in conjunction with removal of the gonads to remove all known sources of sex hormones in patients with hormone dependent carcinoma. Some regression of the neoplasm and clinical improvement of the patient with multiple secondaries has been noted (Taylor, 1954) in patients with advanced carcinoma of the prostate and the breast. Patients selected for adrenalectomy are usually in an advanced stage of disease which may involve hepatic, pleural or pulmonary metastases with resultant diminution in air entry. Low haemoglobin and red cell count are common and should be corrected by blood transfusion. It is essential that cortisone is given pre-operatively in single stage bilateral adrenalectomy, and before the operation for removal of the second adrenal in the two-stage type. It is also advisable to give cortisone before the removal of the first adrenal, in case there is only one gland, or that the second may be replaced by carcinomatous tissue. Intramuscular injection of cortisone in 100-mg doses is given 48 hours, 24 hours, and 1 hour before the scheduled start of operation. Premedication should be atropine or scopolamine with a hypnotic. Before operation, intravenous transfusion is essential; using a three-chambered set, one bottle of dextrose, one plainly labelled bottle of 5 per cent dextrose with 4 ml noradrenaline added and firmly turned off, and one chamber reserved for blood transfusion if necessary.

The operation is usually performed in two stages. The first, oöphorectomy and removal of the right adrenal is carried out about three weeks before removal of the left. For the first stage, the anaesthetized patient is placed supine on the table and oöphorectomy performed through an

abdominal incision. The patient is then turned on to the left side for removal of the right adrenal, the bridge of the table being raised, or a sandbag inserted under the left loin. For the second stage, the removal of the left adrenal, the patient is placed on her right side on the table, and the left loin used for the surgical approach. A loin incision is used for removal of both adrenals, and the 12th and sometimes the 11th rib removed. Incision of the pleura, accidental or designed, may occur.

General anaesthesia is indicated for the operation. Induction is with thiopentone and with the aid of a short-acting relaxant, a cuffed tube is inserted into the trachea. Frequent involvement of the pleura with secondary carcinomatous deposits, presence of pleural fluids, the limitation of respiratory movement by the operative position and the possible opening of the pleural cavity during operation necessitates control of respiration. Therefore, cuff tube, closed circuit anaesthesia and use of the relaxants with gas and oxygen is advisable. Pethidine and further doses of thiopentone may be given when indicated.

It is essential that the blood pressure be recorded throughout the operation; minor falls occur with the hypotensive effect of thiopentone during the induction of anaesthesia and with blood loss. The estimated blood loss from observation of the swabs, packs and sucker contents should be replaced. Occlusion of the veins of the second gland usually causes an abrupt fall in blood pressure. This should be corrected immediately with the noradrenaline solution which is run intravenously as fast as is necessary to restore and maintain pressure. Postoperatively, this transfusion of noradrenaline is maintained until the blood pressure remains level when the drip is discontinued. In some cases, the pressure has not fallen on occlusion of the veins. This may be due to the presence of other adrenal tissue in the body, to handling of the gland and output of hormones before ligating the veins (which maintains pressure), or in the cases of complete replacement of the gland by tumour, to the prior secretory function of noradrenaline by other tissues being established.

Partial Adrenalectomy and Tumour Removal.

Tumour or cortical hypertrophy is found in Cushing's syndrome and treatment consists of excision of the tumour or subtotal adrenalectomy. Anaesthesia is as outlined above. Pre-operative preparation includes administration of 200 mg of cortisone given intramuscularly each day for two days prior to operation. A mild diabetes, which is resistant to insulin, may be present clinically and therefore pre-operative administration of glucose is advisable.

The adrenogenital syndrome of virilism and disordered nitrogen metabolism is also caused by a tumour or hypertrophy of the cortex and the treatment is to excise the tumour or perform a subtotal resection.

The adrenal medulla possesses sympathetic nervous tissue from which a phaeochromocytoma may arise. The treatment is surgical removal, and anaesthesia follows that indicated by Paper and Cahill (1952) and Ward, Riches and Johnson (1952). The clinical picture is typified by

acute attacks of hypertension, and severe hypertension may occur during the anaesthesia, due to the excretion of sympathetic amines from the tumour. This is most likely to occur early in anaesthesia, especially during the positioning of the patient and in the handling of the tumour. Phentolamine is adrendylic and lowers blood pressure if elevation is due to circulating adrenaline and is given with the premedication in a 20-mg dose intramuscularly, and in 10-mg doses before the induction of anaesthesia, before the positioning on the table, and before the tumour is handled.

Some 10 per cent of the tumours are bilateral and a laparotomy through abdominal incision is usually performed unless the diagnosis is certain.

Premedication consists of scopolamine and a sedative. The anaesthetic advocated is thiopentone induction, with phentolamine 10 mg given intravenously; intubation with a cuff tube using a short-acting relaxant; maintenance with gas, oxygen, pethidine, with intermittent thiopentone injections; and the use of continuous suxamethonium in drip form, if respiratory control is made necessary as by pleural puncture.

Drugs which affect myocardial irritability or rate, and produce ventricular arrhythmias in the presence of circulating adrenaline are contra-indicated; thus chloroform, ether, cyclopropane, trilene, flaxidil, and curare are all debarred. Gross irregularity of the pulse may occur during the tumour dissection due to excessive secretion of noradrenaline. If this occurs, procaine amide in 200-mg doses should be administered intravenously. Following ligation of the vascular pedicle of the tumour, some hypotension rapidly occurs and must be immediately corrected by noradrenaline transfusion. When pressure is restored, the slow infusion is continued postoperatively for about twenty-four hours, and until the danger of hypotensive episodes is past.

It will be thus apparent that anaesthesia for adrenalectomy, although not technically difficult, requires careful preoperative preparation and assessment, unremitting observations of the condition, and especially of the blood pressure, of the patient. Patients on cortisone therapy are sensitive to anaesthetic drugs and added caution in their administration is indicated. Blood loss is badly tolerated and death may occur immediately postoperatively from shock in spite of normally adequate care and attention.

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CATARACT EXTRACTION UNDER GENERAL ANAESTHESIA

BY

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SINCE the discovery of cocaine, local analgesia has been extensively used in ophthalmic surgery. In recent years, more interest has developed in general anaesthesia. This followed the introduction of the ultra-short-acting barbiturates and, later, the muscle relaxants. Local analgesia remains, however, the first choice in most ophthalmic centres, particularly for cataract extraction.

The increasing use of supplementary intravenous curare to keep conscious patients at rest and relaxed (Kirby, 1950; Argarwal and Mathur, 1952; Wheeler, 1953) suggests that local analgesia alone is not entirely satisfactory. Apart from inadequate analgesia, other complications may arise. In an investigation into the blood pressure reactions of patients undergoing ophthalmic operations under local analgesia, Frey (1949) found a rise, greater in the older age groups, in which retrobulbar analgesia, with or without adrenaline played no part. A fatal vascular accident from this cause was recorded. Pulmonary collapse after ophthalmic operations under local analgesia has been described (Lane, 1941) whilst nausea and vomiting are not uncommon.

General anaesthesia has therefore been used for all ophthalmic operations in this hospital, and in this paper a series of 190 cataract extractions personally anaesthetized is considered. The operations were of the extracapsular type and in the majority, a conjunctival flap was used. The patients varied in age from 37 to 97. As shown in figure 1, the majority were aged. Hypertension, chronic bronchitis and emphysema, diabetes mellitus and some degree of congestive cardiac failure are common. No patient has been considered unfit for anaesthesia, these conditions calling rather for an adjustment of dosage.

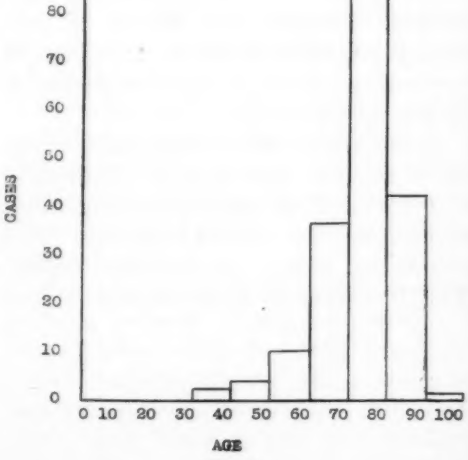

FIG. 1

TECHNIQUE

Premedication consists of morphia $\frac{1}{8}$ grain (8 mg) to $\frac{1}{6}$ grain (10 mg) according to physique and atropine $\frac{1}{100}$ grain (0.65 mg) given by intramuscular injection one hour before operation. Anaesthesia is induced with approximately 0.4 g thialbarbitone sodium ("Kemithal") followed by 70 mg gallamine triethiodide. After inflation with oxygen, a "Portex" endotracheal tube, usually size 10, is inserted under direct vision. The tube is lubricated with an analgesic ointment. Anaesthesia is maintained with nitrous oxide (5 l./min) and oxygen (2 l./min). Respiration is aided if necessary. Supplementary doses of thialbarbitone are given when indicated, e.g. on finger movement. Any troublesome bleeding is controlled by the topical application of adrenaline. On completion of the operation, the tube is slowly removed after the pad and bandage have been applied. In this way, the likelihood of a cough on extubation is diminished.

Complications.

(i) *Haemorrhage.* During the postoperative phase, 11 patients developed haemorrhage with clot formation in the anterior chamber of the eye sufficient to require removal. The anterior chamber was washed out under general anaesthesia in these cases at various times from 24 hours to 7 days after the original operation.

(ii) *Prolapse of the iris.* One case of prolapse of the iris through the wound occured. This was treated by iridectomy.

(iii) *Mental changes.* Temporary postoperative mental changes e.g. confusion, were not uncommon. These changes occur irrespective of the type of anaesthesia and seem peculiar to the operation of cataract extraction (Russell, 1935; Linn et al., 1953).

Deaths.

Three patients died before discharge from hospital. These were aged 78, 82 and 83, and the respective causes of death were inanition, a fracture of the neck of the femur, and bronchopneumonia.

DISCUSSION

If general anaesthesia is to be used, certain requirements must be met. These are:

(i) *The eye must be stationary.* This may appear obvious but in an investigation into the popularity of local analgesia, Macintosh (1938) found that eye movement was a frequently mentioned disadvantage of general anaesthesia.

(ii) *There should be no straining, vomiting or coughing during or after operation.* This cannot be guaranteed but the incidence using modern anaesthetic drugs is low. Vomiting postoperatively is often due to other factors, e.g. psychic, and is not unknown after local analgesia.

(iii) *A reduction of the intra-ocular pressure.* After the lens is removed, vitreous may be lost if the intra-ocular pressure is raised. This must be prevented since the vitreous, which is the transparent gel filling the eye behind the lens, cannot be reformed. Anaesthesia, including the relaxants, affect this pressure by paralysis of the external ocular muscles. A fall in the intra-ocular pressure of almost 50 per cent has been demonstrated by Colle et al. (1931) when these muscles are paralysed by curare, the blood pres-

sure being maintained at a constant level. The intra-ocular pressure varies directly with the capillary blood pressure and therefore can be influenced by the general arterial and venous pressures only in so far as their effect penetrates to the capillary circulation (Duke-Elder, 1938).

(iv) *Surgical access.* This implies endotracheal intubation to ensure control of the airway. Face masks encroach on the operation site. Oral airways with insufflation of oxygen can be used but aided respiration is not then possible and control of the chin is difficult under the towels draping the head and neck.

Thialbarbitone sodium is used rather than thiopentone sodium because it produces less respiratory depression for equivalent depth of anaesthesia. This has been shown experimentally in animals Carrington and Raventós, 1946) and man (Way, 1951). The respiratory activity seen when using this combination of drugs suggests that in many cases of apnoea or respiratory depression thiopentone is responsible, rather than the relaxant.

A relaxant is used (*a*) to facilitate intubation and (*b*) to relax the external ocular muscles and thus lower the intra-ocular pressure. In this series, gallamine triethiodide has been used because it is the shortest-acting relaxant for which an antidote is readily available. Suxamethonium chloride is unsuitable since Hofmann et al. (1953) have demonstrated a rise in the intra-ocular pressure following the administration of this drug.

A small number of operations were carried out using chlorpromazine and other drugs as described by Smith and Fairer (1953). Although the operating conditions were satisfactory, the method was abandoned because of the prolonged postoperative coma. Chlorpromazine is now used only for those particularly prone to vomit.

Experience has shown that cataract extraction under general anaesthesia gives satisfactory results for both patient and surgeon. Vitreous loss has been minimal and complications rare. The wider use of general anaesthesia for this operation is recommended.

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CONTROLLED HYPOTENSION BY EXTRADURAL SPINAL BLOCK UNDER CHLORPROMAZINE COVER*

BY

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VASCULAR hypotension produced by block of the preganglionic sympathetic fibres in the extradural space was first used by Bromage in 1951. The purpose of this paper is to draw attention to some specific benefits obtainable by the use of chlorpromazine as an adjuvant to this technique. One hundred and five patients, aged from 62 to 86 years, provided the material for this study. Most of them were extremely poor risks for general anaesthesia by conventional methods. The operations performed were a variety of major urological, gynaecological, and orthopaedic procedures. In all cases a reduction in surgical haemorrhage produced real benefits to the patient.

During the last two years the following technique has been developed and found satisfactory.

One hour before operation 50 mg chlorpromazine and 100 mg pethidine are given intramuscularly. The patient is always calm and unconcerned but cooperative on arrival in the anaesthetic room. The lumbar extradural space is located by Dogliotti's loss-of-resistance test, and 30 ml of 1.5 per cent lignocaine are injected slowly in intermittent doses within 5 minutes. After this time the patient becomes very drowsy and the blood pressure starts to drop, accompanied at first by a tachycardia. A Trendelenburg tilt of 15 degrees is employed to assist the spread of lignocaine to the upper thoracic segments, and the onset of bradycardia indicates total sympathetic paralysis. The legs are lowered from the hips to obtain postural hypotension, and in this way, a systolic pressure of 60 to 70 mm Hg at heart level is achieved in the majority of cases within 20–30 minutes of starting extradural block. Sometimes this occurs more quickly in the arteriosclerotic patient with hypertension. When the pressure drops below 60 mm Hg the venous return and the cardiac output are improved by raising the legs and increasing the Trendelenburg tilt. The duration of hypotension averaged 2 hours. In no case was it considered necessary to administer a vasopressor drug.

Patients in the hypotensive state were asleep, but the eyelash reflex was always present, and they could easily be roused and responded to questions. The muscles of respiration were apparently not affected by the concentration of lignocaine used, and the respiratory exchange was generally adequate. However, in some cases a marked tendency for the respiratory rate to slow down was observed, developing into a Cheyne-Stokes pattern of breathing with apnoeic intervals of 10 seconds. This phenomenon may be explained by a combined effect of reduced cerebral blood

* Presented at the World Congress of Anaesthesiologists, Scheveningen, September, 5–10, 1955.

flow and depression of the respiratory centre by pethidine and chlorpromazine. Full oxygenation was ensured in such a condition by a B.L.B. mask and insertion of an artificial airway.

The postoperative course of these elderly people was unusually good, and there was no evidence of any damage as a result of the hypotension. Three cases with long established severe myocardial damage made an uneventful recovery. The pre-operative electrocardiographic pattern of myocardial ischaemia in these cases did not deteriorate during or after operation. It is reasonable to suppose that, during the period of hypotension, the probable decrease in the circulation through the affected myocardium was offset by a reduction in cardiac work and oxygen consumption. Until more is known of circulatory changes in vital organs during hypotension it would, however, appear wiser to avoid this technique in patients with coronary arterial disease.

The following complication, which is worthy of mention, may well be explained by overactivity of an unopposed vagus, after paralysis of the sympathetic nervous system. One patient, who was known to have a peptic ulcer, developed malaena, and another patient had one minor episode of haematemesis in the first 24 hours after surgery. Chlorpromazine has been stated to reduce gastric secretions, but these two cases suggest that it has no vagal blocking action.

The only death was in a man of 76 on the seventh postoperative day; he had a total cystectomy for carcinoma and died from uraemia. There appeared to be no association between this technique and the fatal outcome in this patient.

Chlorpromazine, incorporated in the premedication, appeared to have the following advantages:

(1) Controlled hypotension was facilitated. It appeared to supplement the sympathetic paralysis and thus assisted in obtaining and maintaining a low arterial tension.

(2) By reducing the metabolic needs of the tissues the hypotensive technique was made safer. The absence of any postoperative complications of kidney, liver, heart and brain, are clinical grounds for assuming that chlorpromazine has played a major part in protecting the vital organs. In coming to this conclusion, the poor general condition of the patients preoperatively must be stressed again.

(3) It appeared to improve muscular relaxation, for this was comparable with the flaccid paralysis normally achieved with a subarachnoid block.

(4) It eliminated nausea and vomiting commonly seen among conscious patients subjected to the marked physiological derangement of high spinal block.

(5) It potentiated the central sedative action of lignocaine, which accounted, in part at least, for the production of sleep soon after extradural injection was completed. In no case was any supplementary anaesthesia required.

From these observations, it would appear that further use of chlorpromazine in controlled vascular hypotension by extradural block is justified.

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CARLENS CATHETER: A SIMPLE METHOD OF INTUBATION

BY

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Late of Morriston Hospital, Swansea

THE Carlens tube, or double lumen endobronchial catheter, was introduced by Eric Carlens in 1949 for the purpose of making broncho spirometric studies of lung function. Its possibilities in clinical anaesthesia, particularly for thoracic surgery, soon came to be appreciated, and after several years clinical use its advantages and disadvantages have recently been summarized by Rose (1954). The former include prevention of transbronchial spread of infection at operation; independent control of movement and degree of inflation of either or both lungs at will; and control of secretion by suction. The principal disadvantage lies in the small calibre of the endobronchial tubes, with the impediment this offers in some degree to free gaseous exchange.

In addition to this disadvantage, technical difficulty has often been experienced in intubation with the Carlens catheter, mainly owing to the fact that the solid rubber carinal hook does not pass easily through the glottis.

Various manoeuvres have been devised for overcoming this difficulty and the rubber hook is sometimes tied down to the tube proper by means of a slipknot in a silken or nylon thread, which is then released and withdrawn as the rubber hook enters the trachea. The method is, however, rather cumbersome, with the additional possibility of the slipknot loosening prematurely, or refusing to loosen at all after intubation has been successfully achieved.

The following technique has therefore been devised, by means of which intubation is easily and gently performed.

The patient is premedicated in the usual way with papaveratum 22 mg and hyoscine 0.4 mg. In the anaesthetic room a Gordh or similar type needle is inserted into a vein on the dorsum of the hand, and thiopentone administered in the usual dosage of about 400 mg. This is immediately followed by suxamethonium chloride 30–50 mg. After the usual muscle fasciculations when apnoea ensues, ventilation with pure oxygen is performed for 20–30 seconds using a Boyle's machine and mask. Direct laryngoscopy is then performed, and the glottis and trachea liberally sprayed with 1 per cent amethocaine (3–4 ml) using a Mackintosh spray and laryngoscope.

The Carlens tube is then introduced into the glottis, so that the tip of the terminal left endobronchial segment points forwards, the carinal hook lying directly posteriorly. As the tube enters the glottis, the hook engages on the posterior commi-

sure, preventing further progress. The tube is now rotated through 180° so that the carinal hook comes to lie directly anteriorly, when it will be found to pass easily through the intermembraneous part of the glottis into the trachea. Finally, it is rotated back through 90°, so that the tip of the left endobronchial part of the tube slides down the left side of the trachea into the left main bronchus. The hook engages on the carina and intubation is complete. The cuffs are then inflated in the usual way.

Suxamethonium chloride is used as the relaxant, for it is essential to obtain complete relaxation of the glottis with entire absence of spasm, and it is found that even with very large doses of "competitive-blocking" agents, relaxation is not always absolute.

Following intubation, voluntary respiration soon returns, the Carlens tube being tolerated without coughing, and no further relaxant is needed during positioning, towelling up, etc. Finally when all is ready for the operation to commence, control of respiration is secured in the usual way by one of the longer-acting muscle relaxants such as d-tubocurarine.

REFERENCE

Rose, C. E. (1954). *Curr. Res. Anesth.*, **33**, 297.

Brit. J. Anaesth. (1956), **28**, 87

A BABIES' LIGHTWEIGHT SUCTION ENDOTRACHEAL CONNECTOR

BY

L. RENDELL-BAKER

Department of Anaesthetics, Welsh National School of Medicine, Cardiff

THE increasing frequency of operations for tracheo-oesophageal atresia in the newborn, has shown up a deficiency in the armamentarium of the thoracic anaesthetist. These babies invariably require tracheal suction during operation to remove milk, secretion or blood. Unfortunately, the smallest size of any available pattern of endotracheal connector is both too large and too heavy for the 0 and 00 size tubes required for these little patients. The difficulty has been solved by making a connector out of a very light alloy and by slightly modifying the design of Cobb's connector to suit these particular circumstances. The angle has been increased from 90° to 115°, thus suiting the position of the baby's head during the operation. Fine bore polythene tubing has been found satisfactory for use as a suction catheter.

FIG. 1

FIG. 2

ACKNOWLEDGMENT

Considerable help with the design and method of construction was given by Mr. E. K. Hillard, Senior Technician to the Department.

These connectors can be obtained from Messrs. A. Charles King, Limited.

Brit. J. Anaesth. (1956), **28**, 88

A NEW ENDOTRACHEAL HARNESS

BY

F. W. PARKE

Ronkswood Hospital, Worcester

IN using the circle-type absorber for endotracheal anaesthesia, I have been struck by the difficulty in finding a suitable method of retaining the Y-shaped expiratory mount in position.

The great disadvantage of Hudson harness is the trauma caused to the forehead by the pressure exerted on the metal end of the adapter or on the expiratory mount itself, and damage to the supra-orbital nerve from this cause has recently been described by Barron (1955).

The harness described by Levis (1954) is an improvement in this respect, but, like the Hudson harness, the point of fixation is in front of the expiratory mount, and the weight of this latter with its attached corrugated tubes, unless additionally supported, tends to lift the endotracheal tube out of the mouth.

To overcome these difficulties I designed and made the harness here illustrated.

This consists of a metal plate to which are attached two Terry clips and two hooks. It is faced with sorbo rubber, wedged towards the front, backed with strip rubber and moulded to the shape of the forehead. To avoid damage to soft metal expiratory mounts the Terry clips are covered with polythene tubing. Figure 1 shows the harness in position on the forehead.

In use (fig. 2) the Terry clips grasp the transverse parts of the swivel arms of the

FIG. 1

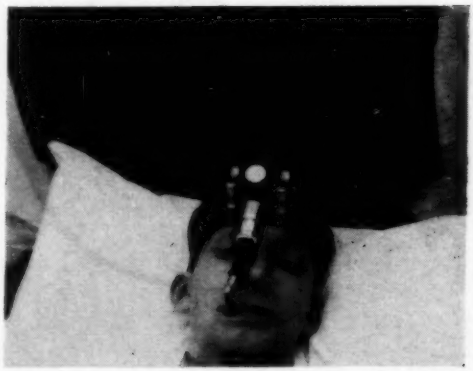

FIG. 2

Y-piece on either side of the expiratory valve and the whole is retained in position by a single rubber strap around the occiput. The retaining hooks being fixed directly to the base plate, there is no drag on the rubber components of the harness.

It has proved extremely satisfactory, the Y-piece expiratory mount being securely fixed no matter what position the patient be in.

ACKNOWLEDGMENT

My thanks are due to Mr. Hiren De, F.R.C.S., for the photographs.

The harness may be obtained from Medical and Industrial Equipment Ltd.

REFERENCES

Barron, D. W. (1955). *Anaesthesia*, **10**, 374.
Levis, R. D. (1954). *Anaesthesia*, **9**, 123.

CORRESPONDENCE

Sir,—Drs. Forrester and Saunders are to be congratulated on their article "Intra-Arterial Thiopentone" (*Brit. J. Anaesth.*, December 1955). One statement therein requires correction. The authors write: "It is interesting to note that this accident has not been observed in a case already anaesthetized." In the case described by me (*Brit. med. J.* (1954), **1**, 393), referred to by the authors, the accident in fact occurred in a patient already anaesthetized with 500 mg thiopentone, during the injection of a supplementary dose in the other arm.

T. D. CULBERT
Manchester

FACULTY NEWS

EIGHTH ANNIVERSARY OF THE FACULTY

The Eighth Anniversary of the Faculty will be held this year on Wednesday, March 21. Arrangements will be made as follows:

3 p.m.—Annual General Meeting, which all Fellows and Members of the Faculty are invited to attend.

4 p.m.—Joseph Clover Lecture, to be given by Dr. K. W. Donald, F.R.C.P.

7.15 p.m. for 7.45 Anniversary Dinner, which may be attended by all Fellows and Members of the Faculty and their guests. Distinguished guests attending the Dinner will include the Minister of Health.

SCIENTIFIC MEETING

A Scientific Meeting of the Faculty will be held on Saturday, May 5, 1956. This time the symposium will be on the Adrenal Gland. Further details will be announced later.

FUTURE COURSES

The Spring Course of Anaesthetic Lectures will be held from April 9 to 28, 1956, and will be open to both D.A. and Final F.F.A.R.C.S. candidates. The fees for this course are as follows:

Lectures	£15 15*s*.
Discussion Groups . . .	£15 15*s*.
Clinical Conferences . . .	£5 5*s*.

EXAMINATION RESULTS

209 candidates presented themselves for the recent D.A. examination 111 of whom passed.

W. F. DAVIS
Secretary

ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.

Licentiate of the Royal College of Physicians

(*Continued from page* 45)

The above account is published in the *Medical Gazette* as communicated by Mr. Solly, but it is clearly not written by him, and it presents a very confused narrative of what occurred. If we are to understand the events in the sequence in which they are related, we must conclude that the patient became insensible and had the operation performed, that he then exhibited alarming symptoms for which cold water was dashed in his face and other measures were employed, and yet after this he struggled for about a minute. This would be a state of things inconsistent, in my opinion, with death from chloroform; but possibly the proper sequence is not observed in detailing what occurred. There is some obscurity also about the amount of chloroform used in connection with what remained on removing the inhaler. If the sponge was adapted to hold a drachm in the proper manner the chloroform could not splash about on its falling, unless there was good deal more than a drachm in it. But whatever was the quantity of chloroform remaining in the sponge, as it was in a condition to splash about, it is difficult to perceive what prevented the liquid chloroform from dropping into the patient's throat, as he lay on his back in bed. Chloroform is as pungent as the essential oils. I have been informed of a case in which a patient was nearly suffocated by one drop falling into the throat; and the narrative of what occurred to Mr. Solly's patient is not at all inconsistent with death from spasm of the glottis arising from this cause. If, however, the patient died from the vapour of chloroform, we must conclude that he inhaled it at one moment not sufficiently diluted with air.

The chloroform in this case was administered by a non-medical person—a sort of surgery-man. After this accident, however, the chloroform in St. Thomas's Hospital was always entrusted to some one belonging to the profession.

Case 13 occurred at Shrewsbury, to a Mrs. Jones, a patient of Mr. Clement, surgeon, who had partly performed the operation of excision of the eyeball, when his patient suddenly died. Mr. Clement has, I believe, not published any account of the case, but the evidence which he gave at the inquest was reported in various local newspapers, and copied into the medical journals. The death was very characteristic of the effects of chloroform vapour not

sufficiently diluted. Mr. Clement is reported to have said: "He gave her but a small dose to commence with, imbibed from a sponge, and then commenced the operation. Finding that did not make her insensible, about a drachm more was poured on the sponge, which she inhaled again for a few seconds. He then went on with the operation, and shortly afterwards heard a peculiar sound, which he could not describe, and she died in a moment; all the attempts to rouse her proved ineffectual. She spoke in Welsh before she died, but so quickly that he did not know what she said; he had no doubt that she died from the effects of the chloroform."*

Case 14 occurred at Berlin. The subject of it was young lady twenty years of age, of good health, well made, and of a good constitution. The chloroform was inhaled for the extraction of a tooth. It was administered on a sponge, covered with a napkin. The dentist who administered it was not a medical man. He made five unsuccessful attempts to extract the tooth under chloroform. Three of these attempts were at nine in the morning, and two about noon, just before the accident. His patient suddenly died almost at the commencement of the last attempt to administer chloroform, stretching herself out, and frothing at the mouth at the moment of death; the countenance at the same time becoming livid.

An examination of the body took place fifty hours after death when putrefaction had set in.

"The lungs presented nothing morbid; the bronchi contained a little bloody froth. The blood was of the colour and consistence of cherry juice. The heart was soft, flabby and collapsed. Its coronary vessels and cavities were empty, and presented the bluish-red discoloration of decomposition."† The other organs were healthy.

Case 15 occurred in the public hospital of Kingston, Jamaica, on January 29, 1850. The name of the patient was William Bryan, his age is not stated, nor the nature of the operation he was about to undergo. He had previously, however, undergone the operation of amputation of the penis, on account of cancer of that organ, but it was performed without chloroform. Mr. Maygarth, the surgeon who administered the chloroform, stated as follows: "I had about a drachm poured on the sponge, and applied it over his mouth and nostrils, but at first not in close contact—at no period was the atmospheric air totally excluded. He bore it badly, and I was frequently obliged to withdraw it, to facilitate his breathing. The stage of excitement which is usual came on, and he struggled and kept away the sponge for some seconds; it was again reapplied, when, after a few more seconds, observing that he made one stertorous inspiration, I removed it altogether. He ceased to breathe; but after some seconds had elapsed, made another inspiration, and this occurred several times, until at length respiration ceased entirely." The measures which were employed were of the usual kind, but were of no avail.

* Journal of Prov. Med. and Surg. Assoc., 1849, p. 698.

† Casper's Wochenschrift, Jan. 12, 1850; and Lond. Med. Gaz., vol. xlv. p. 483.

The brain and its membranes were found to be congested. The lungs were congested, especially posteriorly. The right side of the heart contained dark fluid blood, and the inner surface of its left cavities, and of the aorta were stained with blood. There was some disease of the aortic valves, and the heart had undergone some amount of fatty degeneration."*

Case 16. In February, 1850, a death from chloroform occurred on board ship at the Mauritius. A report of the case was sent to the Board of Ordnance, and also to the Admiralty. The secretary of Sir William Burnett first informed me of the case, and a day or two afterwards I had an opportunity, through the kindness of the late Marquis of Anglesey, of reading the report which was sent to him as Master of the Ordnance, and I made a note of the chief particulars as soon as I got home. As the report was a very able one, it is to be regretted it has not been published. The accident occurred to an artilleryman, aged 24, who required to have the last phalanx of the middle finger removed. In other respects, he was considered to be in good health. Two scruples of chloroform were first poured on the handkerchief with which it was administered, and then one scruple more. It was observed that the face turned pale, and the pulse and breathing ceased, soon after the chloroform was discontinued. The measures which were employed to restore him were of no service. The lungs after death were found to be emphysematous; and, upon enquiry, it was ascertained that he had been short of breath on exertion. The right cavities of the heart were filled with fluid blood. The sinuses of the dura mater contained less blood than usual, and the brain was pale. The medical man reporting the case considered that the emphysema was the cause of death, by interfering with expiration, and thus detaining the vapour; and it must be admitted that, if the vapour were not sufficiently diluted with air, the emphysema might increase the danger. I have, however, administered chloroform in several cases in which emphysema existed to an extreme degree, without any ill effects; consequently, when the vapour is properly diluted with air, this affection appears to be no source of danger.

Case 17 was that of a patient of Professor Carl Santesson, in the Seraphim Hospital at Stockholm. I was indebted to Mr. Paget for my first information about this case, and to Dr. W. D. Moore, of Dublin, for some further particulars respecting it.

The patient, a man thirty years of age, was affected with hydrocele, and there was some suspicion of disease of the testicle. It was consequently intended to operate on the hydrocele by incision, in order that the testicle, if diseased, might be removed. The chloroform was administered in the same way that Professor Santesson had seen it exhibited by Dr. Simpson, except that it was poured on a little cotton, which was placed at the small end of the cone, into which the folded towel he made use of was rolled. About a drachm and a half was first poured on the cotton, and the patient was told to inhale in long and deep inspirations. This quantity being nearly evaporated in two or three minutes, a drachm more was added. After a few

* Edin. Monthly Journal, April 1850, p. 377.

inspirations rigidity and struggling came on: these subsided, but in a little time returned more strongly than before, and the towel was removed from the face until the struggling ceased. The patient, however, not being sufficiently insensible to undergo the operation with the necessary quietness, the towel was reapplied, when, after a few inspirations, the pulse suddenly ceased. The face and the whole surface of the body turned pale, the eyes rolled upwards and inwards, and the breathing became very slow, but full and deep, the intervals between the inspirations becoming longer, until the respiration ceased altogether. The patient died before the operation was begun, and within five minutes from the commencement of inhalation. During the application of various means of resuscitation, including the dropping of cold water *guttatim* on the epigastrium, the breathing returned, and continued for the space of three or four minutes; but the pulse and sounds of the heart did not return.

At the examination, thirty-two hours after death, the dura mater was found to be congested, and there was considerable serous effusion between the membranes of the brain. There were also some bony deposits under the dura mater, and some adhesions of the arachnoid, indicating long standing disease of the membranes.

The heart was of normal size, and flaccid; the vessels on its surface strongly distended with blood. The left ventricle was empty; the left auricle, on the contrary, and the entire of the right side of the heart, with the great veins, were filled with thin uncoagulated blood. In the right ventricle only was a little loose coagulum found. The lungs, posteriorly, were highly congested, exhibiting here and there infiltrations of blood from the size of a pea to that of a small hazel-nut. The pulmonary tissue was otherwise sound; giving, however, when cut into, the odour of chloroform, but more feebly than the brain did. The mucous membrane of the larynx and bronchial tubes were slightly reddened from sanguineous congestion. The blood was everywhere of the same thin juice-like nature.*

Case 18. I am indebted for my information respecting this case to Dr. James Adams, of Glasgow, who was good enough to send me a copy of the notes respecting it, fom the case book of his colleague, Mr. Lyon, in whose practice, in the Glasgow Infirmary, the case occurred, in March, 1850. The patient was a boy seven or eight years old from the Highlands, whose health was considerably impaired by years of suffering from calculus. Mr. Lyon says, " being laid in bed, I placed a piece of lint, moistened with chloroform, near to his face, when, in a few minutes, he ceased crying. I now told my clerk to take charge of the chloroform and introduced the sound. I thought I detected a calculus, but could not hear the click distinctly, in consequence of the patient moaning. One of the bystanders held his hand between my ears and the patient's face, when the click was at once heard. I withdrew the instrument, and was horror-struck with the livid countenance and vacant eye of the patient; the cardiac and radial pulses were gone, and, making one deep gasp, he was to all appearance dead." Artificial respiration and other measures were

* Hygiea, October 1850, p. 602.

employed without effect. "The external jugulars being remarkably turgid, and the face still very livid, the right jugular was opened, when several ounces of dark blood flowed rapidly." This measure, and galvanism, which was applied afterwards, were of no avail.

Case 19. The subject of this case was Alexander Scott, aged thirty-four, a police constable, who died in Guy's Hospital in June 1850, whilst undergoing an operation for the removal of a portion of the right hand. Mr. Cock, the operator, said that he was certain there was no disease about the patient. He described the accident as follows:—"The ordinary machine was used, and, as it had not the effect, witness directed that a napkin should be folded into the shape of a cone, which was applied with chloroform. The occupation of removing a portion of the bone occupied one minute and a half, but before it was completed, the blood which was gushing out, suddenly stopped, when witness directed Mr. Lacy to feel the pulse of deceased, and they found that deceased had expired."*

The sudden stopping of the hæmorrhage shews that, in this case, as in the others, the action of the heart was suddenly arrested. The first attempt to cause insensibility failed in this as in other cases.

Mr. Cock tried to dissuade his patient from having chloroform, severe as the operation would have been without it. In Guy's Hospital and St. Thomas's the medical officers had a strong objection to narcotism by inhalation for the first two or three years after the practice was introduced, and chloroform was used much less generally in these institutions than in any other of the hospitals of London; yet it was precisely in these two hospitals that two deaths from chloroform occurred, before any such accident had happened in any other hospital in this metropolis. The circumstance is worthy of the consideration of those who propose to limit the accidents from chloroform by restricting its use to a few great operations.

In this case the lungs were reported to be extremely congested. Heart flabby, not particularly distended; about two ounces of fluid blood on the right side; not more than half an ounce on the left. Head.—Much congestion of the dura mater; the grey matter of the brain was dark and congested; fluid was found in the subarachnoid space; and a considerable quantity of it in both ventricles. Kidneys congested.*

Case 20 occurred on September 20th, 1850, at the Cavan Infirmary, Ireland. The case occurred in the practice of Dr. Roe, and I am indebted to Dr. Robert Adams, of Dublin, for a manuscript account of it. The name of the patient was James Jones, and his age twenty-four years. Chloroform was exhibited with the intention of performing amputation below the knee, on account of scrofulous disease of the ankle, with ulceration of the cartilages. The patient was reduced to a state of great debility by the disease, and was suffering from hectic fever, but had no cough. The following is Dr. Roe's account of the accident:—

"When placed on the operating table

* Lond. Med. Gaz., vol. xlvi, p. 39.

* Lancet, 1850, vol. ii, p. 21.

the heart's action was very quick and weak, but he did not appear more faint or pale than usual. I then saw Mr. Nalty, the apothecary, measure one drachm of the chloroform in the small minim glass measure, and pour it upon a little folded lint, which was placed in an oval hollow sponge, held in the hand with a small towel. Recollecting I had used this chloroform in another case, and finding some delay in producing the anæsthetic effects, I directed Mr. Nalty to add thirty drops more to that already put on the lint. I then applied the sponge to the patient's nose, directing him to keep his mouth shut, and gave the towel into the care of Dr. Halpin, who was on the opposite side of the table, while I went to prepare myself for the operation. Mr. Bird had scarcely screwed up the tourniquette, which had been previously placed on the thigh, while I was examining the state of the circulation in the tibial arteries, and which could not have occupied one minute,—certainly the patient could not have taken fifteen inspirations,—when Dr. Halpin told me the anæsthetic effects were produced. This struck me as being unusually quick and sudden, and on removing the towel from the face, we saw a slight convulsive action of the left eyelid (the eyelids were partially open), and a small quantity of frothy saliva at the mouth. I felt rather uneasy, but not much alarmed, as Dr. Halpin said he had often seen such symptoms from the effects of chloroform, although I had not met with them. On a more minute examination of the heart, the eyes, muscles of the limbs, &c. we found him dead."

Energetic means were used with a view to restore the patient, but without effect. No inspection of the body took place.

Case 21. The next case of recorded death from chloroform occurred in the Stepney Workhouse. The patient, named John Holden, age not stated, was about to undergo an operation on the penis. It was stated at the inquest that half a drachm of chloroform was administered without effect, and then half a drachm more was applied, when the patient suddenly expired. This death occurred in April 1851.

Case 22 is important, as having given rise to a prosecution. The medical man, an officer de santé, named Kobelt, was accused of homicide, by imprudence, want of precautions, &c. The chloroform was administered on a handkerchief, and the accident occurred as suddenly as any of the others. The husband of the patient stated that the whole process did not last a minute. "I observed attentively," he said, "during this time, and the character that her countenance took all at once made me apprehensive. I spoke of it to the operator, who tranquillized me, and continued to extract the teeth. After the third tooth, however, he partook of my apprehension, suspended the operation, and proceeded to adopt measures indicated by the circumstances." Professor Sédillot, who had to pronounce an opinion on the case, after hearing all the evidence, said, "I do not think that M. Kobelt is guilty of imprudence or of rashness, because that officier de santé has followed a practice very habitually employed, and even recommended, by eminent practitioners, whose example and authority were sufficient to inspire him with security, and

shade him from reproach." The accused practitioner was acquitted. The above remark of Sédillot applied to the plan of causing insensibility very rapidly, as first recommended by Dr. Simpson; and he added some observations to the effect that, when used in a different manner, chloroform is free from danger.

The above case occurred at Strasbourg, on June 10th, 1851. The name of the patient was Madame Simon, and her age thirty-six. After death the lungs were found to be somewhat congested, and emphysematous. Heart flaccid, of middle size; right cavities filled with liquid dark-coloured blood, mixed with some fibrinous clots. The left cavities contained similar blood in much smaller quantity.*

Case 23 occurred on July 8th, 1851, at the Seamen's Hospital, Greenwich. The patient was a light-coloured mulatto, aged forty-five, native of New York. He died during the operation of removing the left testicle, which was disorganized by suppuration. "The chest had been carefully examined a few days previously, both by percussion and auscultation. No physical signs of disease were detected. His pulse was regular and feeble, about seventy. He was rather nervous, and fearful of the operation. No arcus senilis. After taking a glass of wine he commenced the inhalation, twenty minims of chloroform having been poured on a linen cloth. At the expiration of a few minutes, this had been dissipated, producing only very trifling excitement; a second dose, of the same quantity, was then administered in the same way; the man began to sing and shout, his expressions relating to the firing of guns. The second quantity having been exhausted, and the effects of the chloroform becoming more apparent, but sensibility being still perfect, and even intelligence almost unaffected, a third quantity, of ten minims, was poured out, and, afterwards, twenty minims more. Having passed through the usual convulsive stage, and insensibility being established, the further administration of chloroform was desisted from at the end of about seven minutes, though this time is merely guessed at; it might have been more, but was certainly not less. At this time the respiration was unembarrassed, and the pulse regular, and about seventy, with as much volume as before the inhalation. The lips were florid; in fact, the chloroform appeared to have acted in the most benign way. Mr. Busk commenced the operation by an incision through the scrotum, which divided a small arterial branch, and some enlarged veins, from which the blood flowed pretty freely.

* L'Union Médicale, January 29, 1852.

(*To be continued*)

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